NAME OF THE DRUG:

The chemical name for busulfan is 1,4-butanediol dimethanesulfonate, it has a molecular weight of 246.29, its molecular formula is \( \text{C}_6\text{H}_{14}\text{O}_6\text{S}_2 \), CAS No.: 55-98-1 and the chemical structure is:

![Chemical Structure of Busulfan](image)

Myleran tablets contain 2 mg busulfan.

DESCRIPTION:

Busulfan is a white, crystalline powder. It is very slightly soluble in water and ethanol (96%), freely soluble in acetone, in acetonitrile and in chloroform. It has a melting point of 115-118°C.

Each Myleran tablet also contains anhydrous lactose, pregelatinised maize starch, magnesium stearate, hypromellose, titanium dioxide and glycerol triacetate.

ACTIONS:

Myleran in small daily doses of 4 mg, administered orally, depresses both normal and abnormal myeloid tissue. It is this property which has proved to be of value in the treatment of a proportion of cases of chronic myelogenous leukaemia. The drug is more selective than nitrogen mustard or the folic acid antagonists in its effect on the myeloid cells and may be somewhat safer in use; certain patients have received daily doses of 4 mg for as long as a year. In such doses, although it depresses myelopoiesis, it has little effect upon the lymphocytes and platelets, and side effects are absent.

Larger doses, however, depress the platelet count and cause haemorrhagic symptoms, and there is a danger of causing an irreversible depression of the bone marrow which may not become obvious for 4 to 6 months. These effects show the necessity for careful haematological control. The most favourable effects, seen in some cases of chronic myelogenous leukaemia, are rise in the haemoglobin levels, a selective reduction or even disappearance of immature myeloid cells from the blood, a reduction in the cellularity of the bone marrow, a diminution in the size of the enlarged spleen, and pronounced subjective improvement.

INDICATIONS:

Treatment of chronic granulocytic leukaemia. It has been shown to be superior to splenic irradiation when judged by survival times, control of spleen size and maintenance of haemoglobin levels. Although not curative, busulfan reduces the total granulocyte mass, relieves disease symptoms and improves the clinical state of the patient. Busulfan is not useful once blast transformation has occurred.
Busulfan produces prolonged remission in polycythaemia vera. It is especially useful in cases resistant to radiophosphorus ($^{32}$P) and where there is marked thrombocytosis.

Busulfan is useful in selected cases of essential thrombocythaemia and myelofibrosis.

**CONTRAINDICATIONS:**

In view of the seriousness of the indications there are no absolute contraindications.

**PRECAUTIONS:**

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.

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.

Careful attention should be paid to the monitoring of blood counts to avoid the possibility of excessive myelosuppression and the risk of irreversible bone marrow aplasia.

The main side effect of Myleran treatment is bone marrow depression, particularly, thrombocytopenia. Special care must be taken when the initial platelet count is low, and when the count falls during treatment. Administration of Myleran should be stopped immediately at any stage of treatment, if there is a sharp fall in the platelet count or if purpura develops.

If high-dose Myleran is prescribed, patients should be given prophylactic anticonvulsant therapy with preferably a benzodiazepine rather than phenytoin (see ADVERSE REACTIONS and PRECAUTIONS: Interactions with other drugs).

Patients co-prescribed itraconazole or metronidazole with Myleran should be monitored closely for signs of busulfan toxicity. Weekly measurements of blood counts are recommended when coadministering these drugs (see PRECAUTIONS: Interactions with other drugs).

**Monitoring:** Busulfan should not be given to patients who have recently received radiotherapy or other cytotoxic drugs.

Hyperuricaemia and/or hyperuricosuria are not uncommon in untreated patients with chronic granulocytic leukaemia and should be corrected before starting therapy with busulfan. During treatment hyperuricaemia and the risk of uric acid nephropathy should be prevented by adequate prophylaxis.

**Mutagenicity:** Various chromosome aberrations have been noted in cells from patients receiving busulfan. Widespread epithelial dysplasia has been reported.

**Carcinogenicity:** The possibility that busulfan is carcinogenic should be borne in mind. A number...
of malignant tumours have been reported in patients receiving busulfan.

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 Myleran for the treatment of polycythaemia vera and essential thrombocythaemia in view of the drug’s carcinogenic potential. The use of Myleran 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.

**Effects on fertility:** Ovarian suppression and amenorrhoea with menopausal symptoms commonly occur in premenopausal patients.

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.

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

Busulfan interferes with spermatogenesis in experimental animals and there have been clinical reports of sterility, azoospermia and testicular atrophy in man.

**Use in pregnancy:** (Category D)
Busulfan is potentially teratogenic and embryotoxic. Although there have been a number of reported cases where apparently normal children have been born after busulfan treatment during pregnancy, Myleran should be avoided during pregnancy particularly during the first trimester. In every case, the potential benefit to the mother must be weighed against the risk to the fetus.

**Use in lactation:**
Mothers receiving busulfan should not breastfeed.

**Interactions with other drugs:**
Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (See PRECAUTIONS).

The combination of Myleran and thioguanine has resulted in the development of nodular regenerative hyperplasia, portal hypertension and oesophageal varices. 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 myeloblatve effect.

The concomitant systemic administration of itraconazole to patients receiving 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, busulfan in combination with itraconazole or metronidazole is reported to be associated with an increased risk of busulfan toxicity (see PRECAUTIONS).

**ADVERSE REACTIONS:**

The most common side effect is bone marrow depression, particularly thrombocytopenia. Secondary acute leukaemia is common (see PRECAUTIONS: Carcinogenicity).

Gastrointestinal effects such as nausea, vomiting and diarrhoea have been reported rarely. Such intolerance is not a significant problem and can be controlled by giving the daily treatment in divided doses.
Hyperpigmentation is the most common skin reaction and occurs in 5 to 10% of patients, particularly those with a dark complexion. In a few cases a clinical syndrome resembling adrenal insufficiency and characterised by weakness, severe fatigue, anorexia, weight loss, nausea and vomiting, and hyperpigmentation of the skin has developed after prolonged busulfan therapy. The syndrome has sometimes resolved when busulfan has been withdrawn.

Interstitial pneumonitis may occur following conventional dose use and lead to pulmonary fibrosis. Diffuse pulmonary fibrosis with progressive dyspnoea and a persistent nonproductive cough has occurred rarely, usually after prolonged treatment over a number of years. Histological features include atypical changes of the alveolar and bronchiolar epithelium, and the presence of giant cells with large hyperchromatic nuclei. Once pulmonary toxicity is established the prognosis is poor despite Myleran withdrawal and there is little evidence that corticosteroids are helpful. The onset is usually insidious but may also be acute. In a single case pulmonary ossification also occurred.

The lung pathology may be complicated by superimposed infections. It is possible that subsequent radiotherapy can augment subclinical lung injury caused by busulfan. Lens change and cataracts which may be bilateral, have been reported during busulfan therapy.

Corneal thinning has been reported after bone marrow transplantation preceded by high-dose Myleran treatment.

Other reported adverse reactions include urticaria, erythema multiforme, erythema nodosum, alopecia, porphyria cutanea tarda, excessive dryness and fragility of the skin with complete anhydrosis, dryness of the oral mucous membranes and cheilosis, gynaecomastia, cholestatic jaundice, endocardial fibrosis and myasthenia gravis. Most of these are single case reports, and in many a clear cause and effect relationship with busulfan has not been demonstrated. Sjogren's syndrome has also been reported.

An increased cutaneous radiation effect has been observed in patients receiving radiotherapy soon after high-dose Myleran.

A retrospective review of postmortem reports of patients who had been treated with low-dose Myleran for at least two years for chronic granulocytic leukaemia showed evidence of centrilobular sinusoidal fibrosis.

Hyperbilirubinaemia, jaundice, hepatic veno-occlusive disease and centrilobular sinusoidal fibrosis with hepatocellular atrophy and necrosis have been observed after high-dose Myleran treatment.

Convulsions have been observed in adults who have received high-dose Myleran.

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.

**OVERDOSAGE:**

Treatment. The principal toxic effect is on the bone marrow. Survival after a single large dose has been reported, but haematological toxicity is likely to be more profound with chronic overdosage. As there is no known antidote the blood picture should be closely monitored and general supportive measures, together with appropriate blood transfusion, instituted if necessary.
DOSAGE AND ADMINISTRATION:

Chronic granulocytic leukaemia.

Remission induction: The dosage is 0.06 mg/kg daily with a maximum daily dose of 4 mg which may be given as a single dose. Administration of Myleran should be discontinued when the white blood cell count has fallen to between 20,000 to 25,000/mm$^3$ or earlier if the platelet count falls below 100,000/mm$^3$ otherwise there is a considerable risk of causing irreversible bone marrow aplasia since the counts may continue to fall for some time after treatment is stopped. The blood count should be monitored at least weekly during the induction phase and the dose should be increased only if the response after three weeks is inadequate.

Maintenance therapy: Although the white count may be controlled without further therapy for long periods after induction therapy most clinicians use some form of maintenance treatment.

Dosage is usually between 0.5 to 2 mg/day but individual requirements may be much less. The aim is to maintain a white blood count of 10,000 to 15,000/mm$^3$ and blood counts should be performed at least every four weeks.

Polycythaemia vera and essential thrombocythaemia.

Remission induction: The dosage is 4 to 6 mg daily. The total dose required to produce remission varies so that very careful haematological control is essential.

Maintenance therapy: The dosage is approximately half the induction dose but the exact amount must be assessed individually for each patient. Prolonged treatment is necessary, requiring close supervision and frequent blood counts.

Myelofibrosis.

The usual initial dosage is 2 to 4 mg/day, with a lower dose for maintenance. Very careful haematological control is required because of the great sensitivity of the bone marrow in this condition. Myleran is very rarely indicated in children. Provided the outer coating is intact, there is no risk in handling Myleran tablets. The tablets should not be divided.

PRESENTATION:

Myleran tablets are round, normal biconvex white film coated tablets engraved GX EF3 on one face and M on the other.

They each contain 2 mg busulfan and are available in packs of 25* and 100 tablets.

(*not currently distributed in Australia)

SPONSOR:

Aspen Pharmacare Australia Pty Ltd
34-36 Chandos Street
St Leonards NSW 2065

Date of notification of safety-related changes to the TGA: 24 August 1995.
Date of application for tablet reformulation: 22 September 1998
Date of notification of safety-related changes to the TGA: 7 April 1999.
Date of notification of safety-related changes to the TGA: 27 March 2000.
Date of notification of editorial change: 31 May 2000
Date of Notification of safety-related and editorial changes: 6 September 2004
Date of most recent amendment: 31 July 2010