

DATA SHEET

MYLERAN™ Tablets

Busulphan Tablets 2mg

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.

Pharmaceutical form

Film coated tablet.

Clinical particulars

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.

Posology 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 busulphan free days between treatment days. The tablets should not be divided (see Instructions for Use/Handling).

Obese

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 25×10^9 /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 100×10^9 /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 50×10^9 /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 - 15×10^9 /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 busulphan 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.

Busulphan 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 5×10^9 /L or the platelet count below 500×10^9 /L.

Contraindications

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

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

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

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 busulphan.

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)

Safe handling of MYLERAN Tablets:-

See Instructions for Use/Handling.

Mutagenicity:-

Various chromosome aberrations have been noted in cells from patients receiving busulphan.

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

Use During 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 busulphan, have been reported and third trimester exposure may be associated with impaired intra- uterine 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 busulphan 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.

Effects on Ability to Drive and Use Machines

There are no data on the effect of busulphan on driving performance or the ability to operate machinery. A detrimental effect on these activities cannot be predicted from the pharmacology of the medicine.

Interaction with Other Medicinal Products 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 myeloblastic effect.

In patients receiving high-dose busulphan it has been reported that co-administration of itraconazole decreases clearance of busulphan by approximately 20% with corresponding increases in plasma busulphan levels. Metronidazole has been reported to increase trough levels of busulphan by approximately 80%. Fluconazole had no effect on busulphan clearance. Consequently, high-dose busulphan in combination with itraconazole or metronidazole is reported to be associated with an increased risk of busulphan 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 busulphan.

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 ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10,000$ 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 busulphan.

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 busulphan treatment.

Cardiac disorders

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

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 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 bronchial lavage. 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.

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.

Busulphan 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 busulphan 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 multiformae, 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 busulphan.

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 busulphan.

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 busulphan 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 busulphan therapy. The syndrome has sometimes resolved when busulphan has been withdrawn.

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

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 busulphan.

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

Pharmacological properties

Pharmacodynamic Properties

Mode of action:-

Busulphan (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 busulphan on granulocytogenesis 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.

Pharmacokinetic Properties

Absorption:-

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

The area under the curve (AUC) and peak plasma concentrations (C_{max}) of busulphan have been shown to be linearly dose dependent. Following

administration of a single 2 mg oral dose of busulphan, the AUC and C_{max} of busulphan were 125 ± 17 nanograms.h/ml and 28 ± 5 nanograms/ml respectively.

A lag time between busulphan administration and detection in the plasma of up to 2 h has been reported.

High-dose Treatment:-

Busulphan was assayed either using gas liquid chromatography with electron capture detection or by high-performance liquid chromatography (HPLC).

Following oral administration of high dose busulphan (1 mg/kg every 6 h for 4 days), AUC and C_{max} 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:-

Busulphan is reported to have a volume of distribution of 0.64 ± 0.12 L/kg in adults.

Busulphan 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 busulphan was 1.1 : 1.

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

Metabolism and Excretion:-

Busulphan metabolism involves a reaction with glutathione, which occurs via the liver and is mediated by glutathione-S-transferase.

The urinary metabolites of busulphan have been identified as 3-hydroxysulpholane, tetrahydrothiophene 1-oxide and sulpholane, in patients treated with high-dose busulphan.

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

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

Special Patient Populations

Children

The bioavailability of oral busulphan 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 C_{max} 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.

Busulphan is reported to have a volume of distribution of 1.15±0.52 L/kg in children.

When busulphan 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 busulphan clearance. Dosing based on body surface area or adjusted ideal bodyweight should be considered in the obese.

Preclinical Safety Data

Mutagenicity:-

Busulphan 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 busulphan treatment.

Carcinogenicity:-

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

Teratogenicity:-

There is evidence from animal studies that busulphan 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:-

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

Pharmaceutical particulars

List of Excipients**Tablet core:**

Anhydrous lactose
Pregelatinised starch
Magnesium stearate

Tablet coating:

Hypromellose
Titanium dioxide
Triacetin

Incompatibilities

None known.

Shelf Life

36 months

Storage Conditions

Store below 25°C. Keep dry.

Package quantities

100 tablets.

Instructions for Use/Handling**Safe handling of MYLERAN tablets:-**

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.

Medicines Classification

Prescription Only Medicine

Name and address

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Date of preparation

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