BUSULFAN
(Myleran Film Coated Tablets)

Indications
Chronic Myeloid Leukaemia
Polycythaemia Rubra Vera
Essential Thrombocythaemia
Myelofibrosis

Pre-treatment Evaluation
- Document FBC (with film), U&E, LFTs, and Uric Acid
- Document height, weight and body surface area include on prescription.
- Give adequate verbal and written information for patients and relatives concerning patient’s disease, treatment strategy and side effects.
- Obtain written consent from patient or guardian.
- If appropriate, discuss the possibility of pregnancy with female patients of child-bearing age and the need for contraception with both male and female patients.
- If appropriate, discuss potential risk of infertility with patient and relatives.
- Consider intravenous hydration in patients with bulk disease.
- Start Allopurinol if appropriate.

Drug regimen
Supplied as 2mg tablets. Doses should be rounded to nearest 2mg.

CONTINUOUS TREATMENT
Chronic granulocytic leukaemia \(^{(1,2)}\)

Induction in Adults
Dose 0.06mg/kg/day ORAL

Initial daily maximum of 4 mg, which may be given as a single dose.
The blood count must be monitored at least weekly during the induction phase.

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 acceptable levels.

Maintenance in adults:
Dose 0.5 to 2 mg/day ORAL*

*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.

**Polycythaemia vera**
Daily 4 to 6 mg ORAL.

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 Busulfan may be given solely to control the platelet count.

**Myelofibrosis**
Daily 2 to 4 mg ORAL.
Very careful haematological control is required because of the extreme sensitivity of the bone marrow in this condition.

**Essential thrombocytthaemia**
Daily 2 to 4 mg ORAL.

**PULSED TREATMENT**
Single dose 50-75mg ORAL
Repeat as needed after 3-6 months.

**Side Effects**

**Blood and lymphatic system disorders:**
Dose-related bone marrow depression, manifest as leucopenia and particularly thrombocytopenia.
Aplastic anaemia has been reported rarely, typically following long-term conventional doses and also high doses of Busulfan.

**Eye disorders:** Lens changes and cataracts, which may be bilateral

**Pulmonary:** Interstitial pneumonitis following long term conventional dose use, Pulmonary Fibrosis.

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. This usually occurs after prolonged treatment over a number of years. The onset is usually insidious but may also be acute.

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

**Gastrointestinal disorders:** 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**: Hyperbilirubinaemia, jaundice, hepatic veno-occlusive disease and centrilobular sinusoidal fibrosis with hepatocellular atrophy and necrosis.

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.

**Skin and subcutaneous tissue disorders**: Alopecia rare at conventional dose.

Hyperpigmentation †

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 anhidrosis, dryness of oral mucous membranes and cheilosis, Sjogren's syndrome.

† It is often most marked on the neck, upper trunk, nipples, abdomen and palmar creases.

**Reproductive system and breast disorders**: 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.

**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.

Rare: Widespread dysplasia of epithelia.
Seen in a few cases following prolonged Busulfan therapy. The syndrome has sometimes resolved when busulfan has been withdrawn.

**Anti-emetics**
This regimen has low/mild emetic potential

**References**
1. SPC Myelran ,GlaxoSmithKline UK.

**Written by:** Dr Rachel Elliott, Consultant Haematologist

**Authorised by:** Lynne Herring, Haematology Directorate Pharmacist

**Date for review July 2010**