Indication: Patients with essential thrombocythaemia (ET), polycythaemia vera (PV), myelofibrosis (PMF) who are refractory or standard therapy. Patients with CML not able to tolerate or are refractory to standard therapy. Patients with relapsed/refractory AML.

Regimen details:

**For myeloproliferative disorders:**
- Busulfan 4 mg orally once daily for 7 to 14 days according to magnitude of desired effect
- OR
- Busulfan 25 to 40 mg orally STAT according to magnitude of desired effect
- OR
- Busulfan 2 to 4 mg orally daily until blood count starts to fall, then STOP

**For CML Induction:**
- Busulfan 0.06mg/kg orally Daily (max. 4mg/day)

**For CML Maintenance:**
- Busulfan 0.5mg to 2mg orally Daily

**For relapsed/refractory AML:**
- Busulfan Variable dose depending on intent of therapy. Clinician decision.

Busulfan is available as 2mg tablets

Administration: Orally

Premedication: None required

Frequency:

**For myeloproliferative disorders:**
Given as interrupted therapy either 7 to 14 days, a stat dose or until blood count starts to fall. SHOULD NOT BE TAKEN CONTINUOUSLY

**For CML:**
Can be given continuously depending on blood counts.

**For AML:**
Can be given continuously depending on blood counts.

Extravasation: Not applicable

Anti-emetics: Not usually required

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**Reason for Update:** Network Protocol Development

**Version:** 1

**Supersedes:** All other versions

**Prepared by:** Laura Cameron

**Approved by SELCN DTAC Chair: Nic Ketley**

**Approved by Chair Haem TWG: Anil Lakhani**

**Date:** 11th June 2008

**Checked by:** (Network Pharmacist): Jacky Turner

**Date:** 3rd July 2008
Busulfan for myeloproliferative disorders, CML or relapsed/refractory AML

Supportive medication: Consider the use of allopurinol in those patients with raised serum urate and/or history of gout.

Regular investigations: FBC at every visit, may be more frequently as per Consultant.
LFTs, renal profile and thyroid function every 6 months

Dose Modifications

Haematological Toxicity A hypoplastic marrow will develop if treatment is continued in the face of falling counts

Renal Impairment No dose modification necessary

Hepatic Impairment No dose modification necessary

Toxicities: Busulfan causes hyperpigmentation (darkening of the skin) which may become persistent with prolonged therapy. The symptoms usually resolve when busulfan is stopped. In some patients hyperpigmentation is associated with severe weakness, fatigue, anorexia, fatigue and nausea and vomiting and thus mimic Addison’s disease

Hyperuricemia during periods of active cell lysis, which is caused by cytotoxic chemotherapy of highly proliferative tumours of massive burden (e.g., some leukemias and lymphomas), can be minimized with allopurinol and hydration. In hospitalized patients the urine may be alkalized, by addition of sodium bicarbonate to the IV fluids, if tumour lysis is expected.

Pulmonary toxicity is characterized by dyspnea, dry cough, fever and rales. It has distinct pathological and radiographic features (bronchopulmonary dysplasia and pulmonary fibrosis) and is related to prolonged treatment. The total dose for pulmonary toxicity has ranged between 500 and 5700 mg, with a mean of 3000mg. Risk factors include thoracic irradiation. Onset may be 8 months to 10 years after the last dose of busulfan, with a mean onset after 4 years of treatment. Patients with pulmonary toxicity who require anaesthesia should receive the lowest possible concentration of inspired oxygen. The course is rapid in some instances; with progression to pulmonary insufficiency and death. Treatment with 50-100 mg of prednisone may be of benefit.

Pubertal development and gonadal function may be adversely influenced by high dose busulfan therapy in children and adolescents. Patients may require supplementation with appropriate gonadal hormones.

Seizures may occur with high dose busulfan; prophylactic anticonvulsants should be used, preferably benzodiazepines because of the risk of drug interactions with other anticonvulsants.

Drug interactions: Phenytoin (or other agents known to be inducers of cytochrome p450) may reduce absorption of phenytoin, plasma concentrations of busulfan reduced by phenytoin.
Thioguanine (with long-term therapy) can cause hepatotoxicity, oesophageal varices, portal hypertension.
Itraconazole can result in increased effects of busulfan due to reduced busulfan clearance.
Busulfan for myeloproliferative disorders, CML or relapsed/refractory AML

Metronidazole can increase the plasma concentration of busulfan
Clozapine can increase the risk of agranulocytosis, avoid concomitant use

Comments:
- Do not use during pregnancy
- Care in the elderly may be more susceptible to toxicity
- Significantly increased risk of acute myeloid leukaemia when given with other leukaemogenic drugs in particular hydroxycarbamide

References:

Patient Treatment Plan

Regimen details: For myeloproliferative disorders:

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<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Duration</th>
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<tr>
<td>Busulfan</td>
<td>4 mg</td>
<td>orally</td>
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OR

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For CML:
Can be given continuously depending on blood counts

For AML:
Can be given continuously depending on blood counts.

Patient visits:
For myeloproliferative disorders:
Hospital visits every 2 weeks then titrated to a maximum of every 3 months

For CML:
As directed by Consultant, depending on blood counts

For AML:
As directed by Consultant, depending on blood counts

GP may be asked to check FBC

Treatment toxicities:
Significantly increased risk of acute myeloid leukaemia when given with other leukaemogenic drugs in particular hydroxycarbamide

Information can be obtained from the patient information leaflet supplied with the busulfan.

Refer to Cancerbackup leaflet when used to treat leukaemia.

Contact Details: