busulfan

SYNONYM(S): BSF; busulfanum; myelosan

COMMON TRADE NAME(S): Busulfex®, Myleran®

B - Mechanism of Action and Pharmacokinetics

Busulfan is a bifunctional alkylating agent, which has been in clinical use since 1953. It is an alkyl sulfonate and is not chemically related to mechlorethamine. Carbonium ions are rapidly formed after systemic absorption of busulfan leading to alkylation of DNA. This results in breaks in the DNA molecule and possible cross-linking of the twin strands, thus interfering with DNA replication and transcription of RNA. The antitumour activity of busulfan is cell cycle phase-nonspecific. Selective effects on granulocytopoiesis are not well understood.

| Absorption                  | Well absorbed, but large intra-individual variation (mean 68%) Food effect unknown. |
| Distribution               | Rapidly eliminated from plasma and distributed mainly into liver, lungs and brain; crosses placenta. |
| Cross blood brain barrier? | Yes; CSF concentrations appropriately equal to the plasma concentrations |
| PPB                        | 32% (irreversible) |
| Metabolism                 | Extensive hepatic metabolism. CYP3A4 substrate. May induce its own metabolism with repeated administration and at high dose. Mainly metabolized via glutathione conjugation. |
| Active metabolites         | None known |
### Inactive metabolites

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<th>Yes</th>
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</table>

### Elimination

Metabolites excreted mainly in urine. Clearance is higher in obese patients and children than in adults.

- **Urine**: 30-60% within 48 hours (1-2% unchanged)
- **Half-life**: Adults: 2.6 hours

### C - Indications and Status

**Health Canada Approvals:**

For use in combination with other chemotherapeutic agents and/or radiotherapy as a conditioning regimen prior to hematopoietic progenitor cell transplantation, including:

- Acute lymphocytic leukemia
- Acute non-lymphocytic leukemia
- Acute myeloid leukemia
- Chronic myeloid leukemia
- Non-Hodgkin’s lymphoma
- Hodgkin’s lymphoma
- Multiple myeloma
- Myelodysplastic syndrome

### D - Adverse Effects

**Emetogenic Potential:**

- Minimal – No routine prophylaxis; PRN recommended (PO doses < 4mg/day)
- Moderate – Consider prophylaxis daily (PO doses ≥ 4 mg/day)

**Extravasation Potential:** Vesicant

The following adverse effects are observed in patients being treated with conventional doses for CML; consult product monograph for risks with high dose for conditioning.
The major dose-limiting effects of busulfan are **myelotoxicity** and **pulmonary fibrosis** (see Special Precautions). Myelotoxicity may be increased in patients who are recovering from the
effects of prior chemotherapy, or who have received P
32 or radiation to marrow bearing bones.

Pancytopenia caused by busulfan may be more prolonged than other alkylating agents; recovery may take from 1 month to 2 years.

Busulfan causes hyperpigmentation (darkening of the skin), particularly in those with a dark complexion, usually on the neck, upper trunk, nipples, abdomen and palmar creases. It may become persistent with prolonged therapy. The symptoms usually resolve when busulfan is stopped. In some patients, hyperpigmentation is associated with severe weakness, weight loss, anorexia, fatigue, 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 alkalinized, 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 3000 mg. 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, slow in others, with progression to pulmonary insufficiency and death within 6 months for most patients. There is no specific therapy other than discontinuing busulfan; treatment with corticosteroids may not be successful in all cases.

**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.

**Additional adverse effects observed with high dose for bone marrow transplant:**

With BMT dosing, the following adverse effects are common: profound myelosuppression, mucositis, nausea and vomiting, diarrhea/constipation, anorexia, dyspepsia, edema, rash, alopecia, electrolyte imbalances, hyperglycemia, hypertension/vasodilation, tachycardia, CNS (insomnia, anxiety, dizziness, depression, headache) and infection.

**Veno-occlusive disease** may be life-threatening, and occurs after high dose chemotherapy (>16mg/kg), especially when given in combination with other alkylating agents. The incidence may be lower when cyclophosphamide is given 24 hours after busulfan and there appears to be a higher incidence with prior radiation or stem cell transplant, concurrent use of multiple alkylating agents, or multiple cycles of prior chemotherapy.

**Seizures** may occur with high dose busulfan; prophylactic anticonvulsants should be used, especially in high risk patients, preferably benzodiazepines because of the risk of drug interactions with other anticonvulsants, unless specified otherwise in treatment protocol.

Other severe but rare side effects reported with high dose busulfan include cardiac tamponade (used with cyclophosphamide), pericarditis, thromboembolism, hemorrhagic cystitis (when used with
E - Dosing

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, degree of myelosuppression, response and concomitant therapy. Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy.

**Adults:**

**CHRONIC MYELOID LEUKEMIA**

Initial:

**Oral:** 1.8 mg/m² daily
to a maximum of 4mg titrated according to myelosuppression

Maintenance:

**Oral:** 1-3 mg daily intermittently or continuously
Consider when remission lasts for less than 3 months.

**BONE MARROW TRANSPLANT:** Refer to local protocols for details. Consider dosing with adjusted or ideal body weight in obese patients.

**Dosage with Toxicity:**

**CHRONIC MYELOID LEUKEMIA**

Dosage in myelosuppression:

Modify according to protocol by which patient is being treated. In general, busulfan should be held and then dose reduced in the presence of myelosuppression.

- Begin/restart treatment when WBC > 50 x 10⁹/L.
- Since effects on the bone marrow may be delayed and prolonged, hold drug or reduce
Dosage at the first sign of abnormal or exceptionally rapid fall in platelets, hemoglobin, or low white blood cell count.

- Some clinical trials hold treatment when WBC < 20 x 10^9/L or when platelets < 100 x 10^9/L.

Dosage with other toxicity:

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms suggesting pneumonitis</td>
<td>Hold; rule out infection. Discontinue if pneumonitis confirmed.</td>
</tr>
</tbody>
</table>

**Dosage with Hepatic Impairment:**

No information found.

**Dosage with Renal Impairment:**

No information found.

**Children:**

Has been used in pediatric populations (≥ 5 months) for BMT conditioning. Use has not been fully investigated. Refer to specific protocols.

F - Administration Guidelines

**Oral:**

- Self-administration; drug available by outpatient prescription.
- May be taken with or without food. Do not crush or chew.
- Store tablets at room temperature (15 to 30°C).
- Do not divide the tablets; may introduce one or more busulfan-free days between treatment days if the patient’s average daily dose requires partial tablets to be given.
- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment.

**Intravenous:**

- Dilute busulfan before infusion; compatible with D5W or NS.
- Final concentration of busulfan should be approximately ≥0.5 mg/mL.
G - Special Precautions

Other:

Busulfan is contraindicated in patients with hypersensitivity reaction to the drug or any of its components. It should not be used in patients whose disease has demonstrated resistance to busulfan. Use with caution in combination with thioguanine, with compromised bone marrow reserve, prior chemotherapy, radiation or P₃₂.

Patients with pulmonary toxicity undergoing general anaesthesia should not be exposed to high O₂ concentrations.

Tablets contain lactose; carefully consider use in patients with hereditary galactose intolerance, severe lactase deficiency or glucose-galactose malabsorption.

Dialysis or treatment with glutathione could be considered if overdosage occurs.

For high dose busulfan used in BMT, the risk of seizures may be increased in patients with a history of seizure disorders, receiving other potentially epileptogenic drugs or cranial trauma. It is recommended that patients be given prophylactic anticonvulsant therapy preferably with a benzodiazepine, rather than enzyme-inducing anticonvulsants such as phenytoin.

Busulfan is teratogenic, fetotoxic, mutagenic and carcinogenic. Impotence or irreversible loss of fertility can occur. Fetal death or congenital malformations may occur during the first trimester of pregnancy and its use is contraindicated in pregnancy. Intrauterine growth may be retarded or fetal gonads damaged during second and third trimesters. Effective contraception should be used during treatment and for 6 months after the last dose. Breast feeding is not recommended due to the potential secretion into breast milk.

H - Interactions

<table>
<thead>
<tr>
<th>AGENT</th>
<th>EFFECT</th>
<th>MECHANISM</th>
<th>MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin (or other agents known to be inducers of cytochrome p450)</td>
<td>↑ clearance and ↓ steady-state levels of BMT doses of busulfan</td>
<td>Possible induction of hepatic microsomal enzyme oxidation system</td>
<td>Avoid concurrent use unless specified in treatment protocol. If use, monitor busulfan efficacy. May consider</td>
</tr>
</tbody>
</table>
### Anticonvulsants with fewer enzyme-inducing properties.

<table>
<thead>
<tr>
<th>Anticonvulsants</th>
<th>Prolonged apnea</th>
<th>Inhibition of serum cholinesterase</th>
<th>Decrease dose of succinylcholine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thioguanine (with long-term therapy)</td>
<td>Hepatotoxicity, esophageal varices, portal hypertension</td>
<td>Unknown</td>
<td>Caution; monitor if these 2 drugs are given together for long-term therapy</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>↑ toxicity</td>
<td>Possible ↓ in glutathione concentrations in blood and tissue - ↓ clearance of busulfan</td>
<td>Avoid in the 72 hours prior to and following busulfan therapy</td>
</tr>
<tr>
<td>Drugs inducing pulmonary toxicity</td>
<td>↑ risk of toxicity</td>
<td>Additive effects</td>
<td>Use with caution and monitor closely</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>↑ busulfan effect</td>
<td>↓ busulfan clearance (up to 25%)</td>
<td>Close monitoring – modify doses as required.</td>
</tr>
<tr>
<td>Grapefruit juice and other strong CYP3A4 inhibitors</td>
<td>May ↑ plasma level of busulfan</td>
<td>May inhibit CYP3A4 metabolism of busulfan</td>
<td>Avoid concurrent use; Avoid grapefruit and grapefruit juice starting 3 days before and ending 1 day after treatment</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>Veno-occlusive disease (observed with high dose busulfan)</td>
<td>Unknown</td>
<td>Caution; delay cyclophosphamide for 24 hours</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>↑ risk of toxicity</td>
<td>Unknown; significantly increase busulfan levels</td>
<td>Avoid concurrent use</td>
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### Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

**Recommended Clinical Monitoring**

<table>
<thead>
<tr>
<th>Monitor Type</th>
<th>Monitor Frequency</th>
</tr>
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</table>
CBC weekly or more frequent at start of therapy

Pulmonary function tests baseline (at risk patients) and if pulmonary effects are suspected

Clinical toxicity assessment, including pulmonary, infection, bleeding, neurotoxicity, hypersensitivity, tumour lysis syndrome, Addison’s-like symptoms, ophthalmic or cardiac toxicities At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

<table>
<thead>
<tr>
<th>Monitor Type</th>
<th>Monitor Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal and liver function tests</td>
<td>baseline and periodic</td>
</tr>
</tbody>
</table>

J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)
- busulfan - oral tablets

K - References


Hehlmann R, Heimpel H, Hasford J, et al. Randomized comparison of busulfan and hydroxyurea in


June 2019 Updated emetic risk category

Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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