

**DRUG NAME: BUSULFAN****SYNONYM(S):** Busulphan, Busulfanum, Myelosan, BSF**COMMON TRADE NAME(S):** MYLERAN® (oral form),<sup>1</sup> BUSULFEX® (intravenous form)<sup>2</sup>**CLASSIFICATION:** Alkylating agent, cytotoxic<sup>3,4</sup>*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Busulfan is a bifunctional alkylating agent.<sup>2,5,6</sup> Following systemic absorption, carbonium ions are rapidly formed, resulting in alkylation of DNA. This leads to breaks in the DNA molecule as well as cross-linking of the twin strands, resulting in interference of DNA replication and transcription of RNA. The antitumour activity of busulfan is cell cycle phase-nonspecific.

**PHARMACOKINETICS:**

Oral Absorption	highly variable (20-99%) <sup>7,8</sup>	
Distribution	rapidly eliminated from plasma	
	cross blood brain barrier?	yes, CSF: plasma ratio 1.3:1 with BMT doses <sup>9</sup>
	cross placenta	yes
	volume of distribution	0.6-1.0 L/kg
	plasma protein binding	7-55%
Metabolism	extensive hepatic metabolism, <b>with CYP3A4 involvement</b> ; at least 12 metabolites identified with unknown activity	
	active metabolite(s)	none known
	inactive metabolite(s)	25-35% as methanesulfonic acid
Excretion	urine	primarily eliminated as metabolites in urine; 10-50% within 24 h (1-2% unchanged)
	terminal half life	2.3-2.6 h
	clearance	2.5-4.5 mL/min/kg, 95-105 mL/min/m <sup>2</sup>
Gender	no information found	
Elderly	no information found	
Children	volume of distribution	children 1.4-1.6 L/kg
	terminal half life	older children: 2.7-2.8 h younger children: 1.5-2 h
	clearance	older children: 3.0-4.5 mL/min/kg, 90 mL/min/m <sup>2</sup> younger children: 6.8-8.4 mL/min/kg, 120-197 mL/min/m <sup>2</sup>
Ethnicity	no information found	

Adapted from references 5 and 9 unless specified otherwise.

**USES:****Primary uses:**

- \*Conditioning regimen prior to bone marrow transplant
- \*Leukemia, chronic myelogenous

**Other uses:**

- \*Health Canada Therapeutic Products Directorate approved indication

**SPECIAL PRECAUTIONS:**

**Contraindicated if history of hypersensitivity to busulfan or any of its components.**<sup>6</sup>

**Pancytopenia** with a hypoplastic marrow will develop if treatment is maintained despite falling counts.<sup>6,7,9</sup> Counts may continue to fall for a month or more after discontinuation of busulfan. A weekly plot of the WBC count versus time should be carried out using a semi-logarithmic plot, as the rate of drop in the counts will help predict when busulfan should be stopped. Although pancytopenia secondary to busulfan can last from 1 month to 2 or more years, it is generally reversible. Use with caution in patients with compromised bone marrow reserve.

Seizures<sup>6,7,9</sup>: high-dose busulfan used as part of preparative regimens for bone marrow transplantation can cause seizures in adults and children. It is recommended that patients receive a loading dose of phenytoin 24 hours prior to the first dose of busulfan followed by maintenance doses to keep phenytoin serum levels in the therapeutic range. Recommend continuation of phenytoin until 48 hours after the last dose of busulfan.

Mutagenicity<sup>6,7,9</sup>: mutagenic in mammalian *in vitro* mutation tests. Busulfan is clastogenic in human *in vitro* and *in vivo* chromosome tests.

Carcinogenicity<sup>7</sup>: busulfan has been associated with the development of acute leukemia in humans.

Fertility<sup>6,7,9</sup>: impotence or irreversible loss of fertility can occur.

Pregnancy<sup>6,7,9</sup>: FDA Pregnancy Category D. There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk in certain conditions (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). Fetal malformation early in pregnancy, bone marrow depression late in gestation, fetal growth retardation and fetal deaths have been reported in pregnant women receiving therapeutic doses of busulfan. Mild anemia and neutropenia have been reported in a neonate whose mother received busulfan during pregnancy.

Breast-feeding<sup>6,7,9</sup>: not recommended due to the potential for secretion into breast milk.

**SIDE EFFECTS:**

ORGAN SITE	SIDE EFFECT	ONSET			
Dose-limiting side effects are in <b><i>bold, italics</i></b> I = immediate (onset in hours to days); E = early (days to weeks); D = delayed (weeks to months); L = late (months to years)					
allergy/immunology	Type I (anaphylactoid) (rare)	I			
	Type III (serum sickness)	I			
blood/bone marrow	aplastic anemia (rare, may occur with long term use)				L
	<b><i>myelosuppression</i></b> <b><i>with continuous therapy: pancytopenia</i></b> (see special precautions)		E		
	<b><i>with intermittent therapy:</i></b> nadir 11-30 days, recovery 24-54 days		E		
cardiovascular (arrhythmia)	tachycardia	I	E		
cardiovascular (general)	cardiac tamponade (2%)	I			
	endocardial fibrosis (rare)				L
	hypertension	I	E		
	thrombosis (27%)		E		
dermatology/skin	<b><i>extravasation hazard: vesicant</i></b> <sup>10</sup>	I			
	alopecia (rare)		E		
	hyperpigmentation (5-10%)		E	D	
	rash (with BMT dosing)		E		
endocrine	gynecomastia				L
gastrointestinal	abdominal pain	I			
	anorexia	I			
	constipation	I			
	diarrhea (more common with high dose)	I			
	dry mouth	I			
	<b><i>emetogenic potential:</i></b> non-emetogenic (high with BMT dosing)	I			
	nausea	I			
	stomatitis	I			
	Vomiting	I			
	esophageal varices (when used with thioguanine)		E		
	mucositis (with high dose therapy)		E		
hepatic	cholestatic hepatitis, jaundice (rare)				D
	veno-occlusive disease (adult 25%; children 8%, with BMT doses)		E		
infection	infections		D		
metabolic/laboratory	hyperglycemia (with IV dose)	I			
	hypokalemia	I			
	hypomagnesemia	I			
	hypophosphatemia	I			
neurology	seizures (10%, with BMT doses)	I			
	dizziness	I			
ocular/visual	cataracts (rare)				L

ORGAN SITE	SIDE EFFECT	ONSET		
pain	arthralgia (with IV dose)		E	
	back pain		E	
	myalgia		E	
pulmonary	pulmonary dysplasia with fibrosis (rare)			L
renal/genitourinary	elevated BUN		E	
	dysuria	I		
	elevated serum creatinine		E	
	hematuria	I		
	hyperuricemia (during periods of active cell lysis)	I		
	oliguria	I		
secondary malignancy	acute leukemia			L
sexual/reproductive function	infertility			L
	delayed pubertal development			L
	decreased gonadal function			L
	ovarian suppression, amenorrhea, menopausal symptoms			L

Side effects adapted from references 1,2,6 unless specified otherwise.

**With BMT dosing**, the following adverse effects are common<sup>6</sup>: mucositis/stomatitis (85%), fever (83%), nausea and vomiting (72%), rash (67%), diarrhea (58%) and infection (31%)

**Hyperpigmentation**<sup>5</sup>: Busulfan may cause hyperpigmentation (darkening of the skin), which may become persistent with prolonged therapy. Usually involves elbows, knees and skin creases. Symptoms mimic Addison's disease and usually resolve when busulfan is stopped.

**Hyperuricemia** during periods of active cell lysis, which is caused by cytotoxic chemotherapy of highly proliferative tumours of massive burden (eg, 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**<sup>5</sup>: Characterized by dyspnea, dry cough, fever and rales. It has distinct pathological and radiographic features and is related to prolonged treatment. The incidence of clinical symptoms is 3%. The total dose for pulmonary toxicity has ranged between 500 and 5700 mg, with a mean dose of 3000 mg. Pulmonary toxicity has not been reported with doses less than 500 mg. Risk factors include thoracic irradiation. The course is rapid in some instances, slow in others. Progression to pulmonary insufficiency and death occurs in most patients. Although no definitive therapy exists, treatment with 50-100 mg of prednisone and discontinuation of busulfan may be of some benefit.

Pubertal development and gonadal function<sup>5</sup>: Children and adolescents may be adversely influenced by high dose busulfan therapy. Patients may require supplementation with appropriate gonadal hormones.

Veno-occlusive disease<sup>5</sup>: Possible risk factors include doses greater than 16 mg/kg and concurrent use of multiple alkylating agents. A clear cause and effect relationship with busulfan has not been demonstrated. Periodic measurement of liver function tests and bilirubin is suggested.

**INTERACTIONS:**

AGENT	EFFECT	MECHANISM	MANAGEMENT
acetaminophen <sup>7,9</sup>	may decrease busulfan clearance if given < 72 h before or at the same time as busulfan	possible reduction in glutathione concentrations in blood and tissue	use with caution in 72 h prior to and following busulfan therapy
grapefruit juice <sup>11</sup>	may increase plasma level of busulfan	may inhibit CYP3A4 metabolism of busulfan in the intestinal wall	avoid grapefruit and grapefruit juice starting 3 days before and ending 1 day after treatment
itraconazole <sup>7,12</sup>	increase busulfan levels	unknown	monitor for increased busulfan toxicity and adjust busulfan dose as needed; when indicated, fluconazole may be a safe alternative to itraconazole
phenytoin <sup>7</sup>	increased clearance and decreased steady-state levels of BMT doses of busulfan	possible induction of hepatic microsomal enzyme oxidation system	avoid concurrent use unless specified in treatment protocol
succinylcholine <sup>6</sup>	prolonged apnea	inhibition of serum cholinesterase	decrease dose of succinylcholine
thioguanine (with long-term therapy) <sup>9</sup>	hepatotoxicity, esophageal varices, portal hypertension	unknown	monitor if used concurrently for long-term therapy

**SUPPLY AND STORAGE:**

**Tablets:** 2 mg; store at room temperature (15-30°C).<sup>1</sup> Keep dry and protect from light.

**Injection:** 60 mg ampoule (single use); each mL contains 6 mg busulfan. Also contains dimethylacetamide and polyethylene glycol. Keep refrigerated between 2-8°C.<sup>2</sup>

**SOLUTION PREPARATION AND COMPATIBILITY:**

For basic information on solution preparation and compatibility, see [Chemotherapy Chart in Appendix](#).

**Diluted solution for infusion<sup>2</sup>:** Compatible with D5W or NS. Stable for 8 hours in NS or D5W at room temperature; stable for 12 hours in NS if refrigerated. Final concentration of busulfan should be approximately  $\geq 0.5$  mg/mL.

**Compatibility<sup>1,2</sup>:** It is recommended that busulfan not be mixed with other drugs.

**PARENTERAL ADMINISTRATION:**

BCCA administration guideline noted in ***bold, italics***

Subcutaneous	not recommended <sup>2</sup>
Intramuscular	not recommended <sup>2</sup>
Direct intravenous	not recommended <sup>2</sup>
<b><i>Intermittent infusion</i></b>	<b><i>via central line over 2 h for 0.8 mg/kg dose, and over 3–4 h for 3.2 mg/kg dose<sup>13-15</sup></i></b>

BCCA administration guideline noted in ***bold, italics***

Continuous infusion	no information found
Intraperitoneal	no information
Intrapleural	no information
Intrathecal	investigational <sup>16</sup>
Intra-arterial	no information
Intravesical	no information

**DOSAGE GUIDELINES:**

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of white blood cell count. Dosage may be reduced and/or delayed in patients with bone marrow depression due to cytotoxic/radiation therapy.

**Adults:**BCCA usual dose noted in ***bold, italics***

<i>Oral</i> <sup>6,7,9</sup> :	Initial dose:	0.06 mg/kg or 1.8mg/m <sup>2</sup> once daily; 4-8 mg (range 1-12 mg) PO once daily (12-20 weeks) <sup>1</sup>
	Maintenance dose:	1-3 mg PO once daily (range 2 mg once weekly to 4 mg once daily)
	<i>Bone marrow transplant:</i>	0.8-1 mg/kg PO every 6 hours for 4 days for a total of 16 doses; may be used in combination with other drugs
<i>Intravenous</i> <sup>5,14,15</sup> :	<i>Bone marrow transplant:</i>	<b>3.2 mg/kg IV once daily for 4 days</b> or 0.8 mg/kg IV every 6 hours for 16 doses <sup>13,14</sup>
<i>Dosage in myelosuppression:</i>	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"	
<i>Dosage in renal failure</i> <sup>9</sup> :	no information found	
<i>Dosage in hepatic failure</i> <sup>9</sup> :	no information found	
<i>Hemodialysis</i> <sup>7,9,17,18</sup> :	removed by dialysis	
<i>Dosage in obese patients</i> <sup>9</sup> :	dose based on adjusted ideal body weight	

**Children:**

<i>Oral</i> <sup>9</sup> :	<i>Initial dose:</i>	0.06- 0.12 mg/kg or 1.8-4.6 mg/m <sup>2</sup> PO once daily
	<i>Maintenance dose:</i>	titrate maintenance dose (continuous or intermittent) to maintain WBC from 15-20 x 10 <sup>9</sup> /L
	<i>Bone marrow transplant:</i>	1 mg/kg PO every 6 hours for 4 days for a total of 16 doses
<i>Intravenous</i> <sup>2,5</sup> :	dose not determined	

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