DRUG NAME: Busulfan

SYNONYM(S): Busulphan, Busulfanum, Myelosan, BSF

COMMON TRADE NAME(S): MYLERAN® (oral)[1]; BUSULFEX® (intravenous)[2]

CLASSIFICATION: Alkylating agent

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Busulfan is a bifunctional alkylating agent.[3-5] 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%)[6,7]	
Distribution	rapidly eliminated from plasma	
	cross blood brain barrier?	yes, CSF: plasma ratio 1.3:1 with BMT doses[8]
	cross placenta	yes
	volume of distribution	0.6-1.0 L/kg
	plasma protein binding	7-55%
Metabolism	extensive hepatic metabolism, via conjugation with glutathione[9]; 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^2
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^2 younger children: 6.8-8.4 mL/min/kg, 120-197 mL/min/m^2

Adapted from references[5,10] 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:

Contraindications:
- history of hypersensitivity to busulfan or any of its components[5]

Caution:
- ***Pancytopenia*** with a hypoplastic marrow will develop if treatment is maintained despite falling counts. 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.[5,6,8]
- Busulfan may cause ***seizures*** in adults and children when high-dose busulfan is used as part of preparative regimens for bone marrow transplantation. 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.[5,6,8]

Special populations:
- Pubertal development and gonadal function in ***children and adolescents*** may be adversely influenced by high dose busulfan therapy. Patients may require supplementation with appropriate gonadal hormones. [3]
- Therapeutic drug monitoring using the measurement of the area under the plasma concentration curve (AUC) is often utilized for dose adjustment in ***children r***eceiving high dose busulfan therapy prior to bone marrow transplant. Refer to protocol by which patient is being treated.[11-13]

Carcinogenicity: Busulfan has been associated with the development of acute leukemia in humans.[6]

Mutagenicity: Mutagenic in mammalian *in vitro* mutation tests. Busulfan is clastogenic in human *in vitro* and *in vivo* chromosome tests.[5,6,8]

Fertility: Impotence or irreversible loss of fertility can occur.[5,6,8]

Pregnancy: FDA Pregnancy Category D.[5,6,8] 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: not recommended due to the potential for secretion into breast milk.

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important. When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	Type I (anaphylactoid) (rare)
	Type III (serum sickness)
blood/bone marrow	aplastic anemia (rare, may occur with long term use)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	myelosuppression with continuous therapy: pancytopenia (see special precautions)
	myelosuppression with intermittent therapy: nadir 11-30 days, recovery 24-54 days
cardiovascular (arrhythmia)	tachycardia
cardiovascular (general)	cardiac tamponade (2%)
	endocardial fibrosis (rare)
	hypertension
	thrombosis (27%)
dermatology/skin	*extravasation hazard:* vesicant[14]
	alopecia (rare)
	hyperpigmentation (5-10%)
	rash (with BMT dosing)
endocrine	gynecomastia
gastrointestinal	*emetogenic potential*: non-emetogenic (high with BMT dosing)
	abdominal pain
	anorexia
	constipation
	diarrhea (more common with high dose)
	dry mouth
	nausea
	stomatitis
	vomiting
	esophageal varices (when used with thioguanine)
	mucositis (with high dose therapy)
hepatic	cholestatic hepatitis, jaundice (rare)
	veno-occlusive disease (adult 25%; children 8%, with BMT doses
infection	infections
metabolic/laboratory	hyperglycemia (with IV dose)
	hypokalemia
	hypomagnesemia
	hypophosphatemia
neurology	seizures (10%, with BMT doses)
	dizziness
ocular/visual	cataracts (rare)
pain	arthralgia (with IV dose)
	back pain
	myalgia
pulmonary	pulmonary dysplasia with fibrosis (rare)
renal/genitourinary	elevated BUN
	dysuria
	elevated serum creatinine
	hematuria
	hyperuricemia (during periods of active cell lysis)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	oliguria
secondary malignancy	acute leukemia
sexual/reproductive function	infertility
	delayed pubertal development
	decreased gonadal function
	ovarian suppression, amenorrhea, menopausal symptoms

Side effects adapted from references[4,15] unless specified otherwise.

The following adverse effects are common ***with BMT dosing*** [5]: mucositis/stomatitis (85%), fever (83%), nausea and vomiting (72%), rash (67%), diarrhea (58%) and infection (31%).

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.[3]

Hyperuricemia during periods of active cell lysis is caused by cytotoxic chemotherapy of highly proliferative tumours of massive burden (eg, some leukemias and lymphomas), and 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[3] is 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.

Possible risk factors for ***veno-occlusive disease*** 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.[3]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
acetaminophen[6,8]	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
itraconazole[6,16]	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[6]	increased clearance and decreased steady-state levels of BMT doses of	possible induction of hepatic microsomal enzyme oxidation system	avoid concurrent use unless specified in treatment protocol

AGENT	EFFECT	MECHANISM	MANAGEMENT
	busulfan		
succinylcholine[5]	prolonged apnea	inhibition of serum cholinesterase	decrease dose of succinylcholine
thioguanine (with long-term therapy)[8]	hepatotoxicity, esophageal varices, portal hypertension	unknown	monitor if used concurrently for long-term therapy

SUPPLY AND STORAGE:

***Oral**:* Aspen Pharmacare Canada Inc. supplies busulfan as 2 mg film coated tablets. Store at room temperature. Tablets contain lactose.[1]

***Injection**:* SteriMax Inc. supplies busulfan as 60 mg single-use (preservative free) vials in a concentration of 6 mg/mL. Refrigerate. Vials contain dimethylacetamide (DMA).[17]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BC Cancer administration guideline noted in ***bold***, ***italics***

Subcutaneous	not recommended[4]
Intramuscular	not recommended[4]
Direct intravenous	not recommended[4]
Intermittent infusion	***via central line[18-20]:*** • over 2 h for 0.8 mg/kg dose • ***over 3-4 h for 3.2 mg/kg dose***
Continuous infusion	no information found
Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	investigational[21]
Intra-arterial	no information found
Intravesical	no information found

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:

BC Cancer usual dose noted in ***bold, italics***

Oral[5,6,8]*:*	initial dose:	0.06 mg/kg or 1.8mg/m^2 once daily; 4-8 mg (range 1-12 mg) PO once daily (12-20 weeks)[22]
		Note: higher doses (eg, 8-12 mg) should only be used by physicians experienced with the use of busulfan
	maintenance dose:	1-3 mg PO once daily (range 2 mg once weekly to 4 mg once daily)
		Note: Treat for at least 3 weeks. Continuous dosing should be considered when remission lasts for less than 3 months
	bone marrow transplant:	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
Intravenous[3,19,20]*:*	bone marrow transplant:	***3.2 mg/kg IV once daily for 4 days*** or 0.8 mg/kg IV every 6 hours for 16 doses[18,19]
Dosage in myelosuppression:	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"	
Dosage in renal failure[8]*:*	no information found	
Dosage in hepatic failure[8]*:*	no information found	
Hemodialysis[6,8,23,24]*:*	removed by dialysis	
Dosage in obese patients[8]*:*	dose based on adjusted ideal body weight	

Children:

Oral[8]*:*	initial dose:	0.06- 0.12 mg/kg or 1.8-4.6 mg/m^2 PO once daily
	maintenance dose:	titrate maintenance dose (continuous or intermittent) to maintain WBC from 15-20 x 10^9/L
	bone marrow transplant:	1 mg/kg PO every 6 hours for 4 days for a total of 16 doses
Intravenous[3,4]*:*	dose not determined	

REFERENCES:

1. Aspen Pharmacare Canada Inc. MYLERAN® product monograph. Toronto, Ontario; 12 January 2017.
2. Otsuka Pharmaceutical Inc. BUSULFEX® product monograph. Saint Laurent, Quebec; 10 March 2017.
3. Reilly C editor. Drug Facts and Comparisons. St. Louis, Missouri: Wolters Kluwer Health Inc; 2003.
4. Orphan Medical Inc. Busulfex product monograph. 19 August 1999.
5. Repchinsky C editor. Compendium of Pharamcueticals and Specialties. Ottawa, Ontario, Canada: Canadian Pharmacists Association; 2003.
6. Busulfan. USP DI. Volume 1. Drug information for the health care professional. 20th ed. Englewood, Colorado: Micromedex, Inc.; 2002.
7. Schuler US, Ehrsam M, Schneider A, et al. Pharmacokinetics of intravenous busulfan and evaluation of the bioavailability of the oral formulation in conditioning for haematopoietic stem cell transplantation. Bone Marrow Transplantation 1998;22(3):241-4.
8. McEvoy G editor. American Hospital Formulary System Drug Information. Bethesda: American Society of Health System Pharmacists; 2003.
9. Triton Pharma Inc. MYLERAN® product monograph. Concord, Ontario; 29 November 2010.
10. Mehalik C editor. Handbook of Clinical Drug Data. Hamilton, Illinois: Appleton and Lange; 1999.
11. AHFS Drug Information® (database on the Internet). Busulfan. Lexi-Comp Inc., 27 March 2014. Available at: http://online.lexi.com. Accessed 29 April 2014.
12. Roberta Esau. Personal communication. Pharmacist, BC Children's Hospital; 24 April 2014.
13. Jeff Davis MD. Personal communication. Pediatric Oncologist, BC Children's Hospital; 24 April 2014.
14. Borje S Andersson (MD, PhD), Department of Blood and Marrow Transplantation, University of Texas, MD Anderson Cancer Center, Houston, Texas. Personal Communication. April 2003.
15. GlaxoSmithKline Inc. Myleran product monograph. Mississauga, Ontario; July 2002.
16. Hebel S editor. Drug Interaction Facts. St Louis: Medifor Inc; 2003.
17. SteriMax Inc. Busulfan for injection product monograph. Oakville, Ontario; 4 May 2017.
18. Andersson BS, Gajewski J, Donato M, et al. Allogeneic stem cell transplantation (BMT) for AML and MDS following i.v. busulfan and cyclophosphamide (i.v. BuCy). Bone Marrow Transplantation 2000;25(Suppl 2):S35-8.
19. Russell JA, Tran HT, Quinlan D, et al. Once-daily intravenous busulfan given with fludarabine as conditioning for allogeneic stem cell transplantation: study of pharmacokinetics and early clinical outcomes.[comment]. Biology of Blood and Marrow Transplantation 2002;8(9):468-76.
20. Fernandez HF, Tran HT, Albrecht F, et al. Evaluation of safety and pharmacokinetics of administering intravenous busulfan in a twice-daily or daily schedule to patients with advanced hematologic malignant disease undergoing stem cell transplantation.[comment]. Biology of Blood and Marrow Transplantation 2002;8(9):486-92.
21. Archer GE, Sampson JH, McLendon RE, et al. Intrathecal busulfan treatment of human neoplastic meningitis in athymic nude rats. Journal of Neuro-Oncology 1999;44(3):233-41.
22. GlaxoSmithKline Inc. Myleran product monograph. Research Triangle Park, North Carolina; April 2003.
23. Stein J, Davidovitz M, Yaniv I, et al. Accidental busulfan overdose: enhanced drug clearance with hemodialysis in a child with Wiskott-Aldrich syndrome. Bone Marrow Transplantation 2001;27(5):551-3.
24. Ullery LL, Gibbs JP, Ames GW, et al. Busulfan clearance in renal failure and hemodialysis. Bone Marrow Transplantation 2000;25(2):201-3.