DRUG NAME: Melphalan

SYNONYM(S): L-PAM,[1] L-Sarcolysin,[2] Phenylalanine Mustard,[1-5] Phenylalanine Nitrogen Mustard[2]

COMMON TRADE NAME(S): ALKERAN®

CLASSIFICATION: alkylating agent[4]

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

MECHANISM OF ACTION:

Melphalan, a bifunctional nitrogen mustard-derivative alkylating agent, is the L-isomer of mechlorethamine.[5] Melphalan inhibits DNA and RNA synthesis via formation of interstrand cross-links with DNA, likely binding at the N^7 position of guanine.[4] Melphalan is cell cycle phase-nonspecific.[1,4] Melphalan also has immunosuppressive properties.[5]

PHARMACOKINETICS:

Table refers to intravenous (IV) dosing except where specified.

Oral Absorption	highly variable and incomplete[5]; bioavailability decreases with repeated doses[6]; presence of food delays time to achieve peak plasma concentrations and reduces AUC by 39-45%; time to peak concentration[6]: 1-2 h	
Distribution	cross blood brain barrier?	low concentrations in CSF; plasma:CSF concentrations 10:1 to 100:1
	volume of distribution	0.5 L/kg; approximates total body water
	plasma protein binding	60-90%
Metabolism	not actively metabolized; primarily eliminated from plasma by nonenzymatic spontaneous hydrolysis; some hepatic conjugation to glutathione[6,7]; renal clearance is not a major route of elimination	
	active metabolite(s)	no information found
	inactive metabolite(s)	monohydroxy- and dihydroxy-melphalan
Excretion	urine	10 ± 6% as melphalan within 24 h; 20-35% of drug and metabolites excreted within 24 h[5]
	feces	20-50% within 6 days[5,6]
	terminal half life[6]	1.2-1.5 h oral: 1-1.25 h
	clearance	250-325 mL/min/m^2; considerable interindividual variation[5]

Adapted from standard reference[4] unless specified otherwise.

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USES:

Primary uses:	***Other uses:***
*Multiple myeloma	Breast cancer[1,5]
*Ovarian cancer	Conditioning regimen pre-autologous and allogenic BMT[1,4,8,9]
	Melanoma (hyperthermic isolated limb perfusion)
	Neuroblastoma[2,2,3,6]
	Rhabdomyosarcoma[1,7,9]
	Waldenstrom's macroglobulinemia[1]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:

- Patients with a history of skin rash with other alkylating agents (e.g., chlorambucil) may have increased risk of rash with melphalan.[4]
- Generally melphalan should not be used concurrently with radiation,[4] however melphalan has been used with radiation for the treatment of multiple myeloma,[10]
- Administer with caution in patients with bone marrow suppression, and/or in patients whose bone marrow reserve may be compromised by recent chemotherapy or radiation.[4]
- Patients with renal impairment are at risk for uremic marrow suppression; severe leukopenia may occur.[4]
- All myeloma patients should be screened for ***Hepatitis B (HBV) reactivation***[11]; for recommended HBV screening and prophylaxis, see BC Cancer Protocol SCHBV ***Hepatitis B Virus Reactivation Prophylaxis***[12]

Carcinogenicity: Melphalan is carcinogenic.[4]

Mutagenicity: Mutagenic in Ames test and mammalian *in vitro* mutation test.[13,14] Melphalan is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[4]

Fertility: Both reversible and permanent sterility and infertility have been reported with melphalan.[1,4] These effects may be related to the dose and length of therapy[1,8]; the total dose below which there is no risk to fertility has not been established. Prediction of the degree of testicular or ovarian function impairment is complicated by the common use of combination therapy.[1,4] In animal studies, melphalan showed reproductive effects attributed to cytotoxicity in specific male germ cell stages and induced dominant lethal mutations and heritable translocations in post-miotic germ cells, particularly in mid to late stage spermatids. In female study animals, a reduction in the proportion of productive females was associated with an induced reduction in the number of small follicles and occurred simultaneously with a decline in litter size.[15]

Pregnancy: In animal studies, a pronounced reduction in litter size occurred within the first post-treatment interval, followed by an almost complete recovery. However, a gradual decline in litter size occurred thereafter.[15]

Breastfeeding is not recommended due to the potential secretion into breast milk.[4]

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.[16] When placebo-controlled trials are available, adverse events are included if the incidence is ≥ 5% higher in the treatment group.

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The following table is based on IV and oral data using several different dosing schedules unless otherwise specified. For information regarding hyperthermic isolated limb perfusion, see paragraph following Parenteral Administration table.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	hypersensitivity reactions including anaphylaxis (2%); typically occurs after several courses of IV therapy,[5,17] see paragraph following **Side Effects** table
	vasculitis
blood/bone marrow/ febrile neutropenia	anemia[5] (11-60%, severe 2-12%)[17]; typically occurs 6-8 weeks after initiation of therapy; hemolytic anemia also reported
	immunosuppression,[1] leukopenia, neutropenia (5-79%, severe 3-37%)[8,17]; dose related, variable onset,[2] has occurred after 5 days[5,8]; typically occurs 2-3 weeks after initiation of therapy
	thrombocytopenia (5-55%, severe 3-43%),[8,17] typically occurs 2-3 weeks after initiation of therapy[5]
cardiovascular (arrhythmia)	atrial fibrillation; after high-dose melphalan[1]
cardiovascular (general)	hypotension[7]
constitutional symptoms	fatigue[16]
dermatology/skin	***extravasation hazard: vesicant***[18]
	alopecia (7-9%, severe 0.5%)[17]; dose related, 100% after high-dose melphalan
	injection site reaction (50%); burning,[7] irritation, pain, ulceration, flushing, and sensation of warmth and/or tingling, typically mild and resolves in a few hours without treatment; skin necrosis rarely requiring skin grafting has occurred[5,7]
	maculopapular and urticarial rash,[5] dermatitis, and pruritis[5]
endocrine	antidiuretic hormone secretion abnormality[6]
gastrointestinal	***emetogenic potential***[19]***: dose related;*** rare for low dose oral; highly emetogenic for high dose (≥100 mg/m^2) and stem-cell or bone marrow transplantation[20-24]
	anorexia[7]
	diarrhea; dose related, typically occurs 1 week after high-dose melphalan
	nausea and vomiting; dose related[5]; (≤30%, severe <2%)[6,8,17]; (30-90% after high-dose melphalan)[6,23]
	stomatitis (≤50%)[1,25]; dose related[8]
hemorrhage	hemorrhage[17] (severe 1-3%)[17]
hepatobiliary/pancreas	hepatic toxicity; after high-dose melphalan[17]
infection	infection not otherwise specified[17] (5-21%, severe 2-14%)[17]
metabolic/laboratory	abnormal liver function tests; elevated transaminases[6]; usually mild, typically seen with high-dose melphalan[17]
	hyperuricemia; typically seen early after starting treatment in patients with renal damage
	elevated serum creatinine
	hyponatremia[1]; after high-dose melphalan[1]
neurology	neuropathy[17] (2%)[17]

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	radiation myelopathy[6]
	seizure[1]; in patients with renal failure[1]
pulmonary	pulmonary fibrosis/interstitial pneumonitis; see paragraph following **Side Effects** table
renal/genitourinary	bladder irritation/cystitis[6]
	renal failure[1]
secondary malignancy	carcinoma; cumulative dose and duration dependent
	acute leukemia (2%-20%); cumulative dose and duration dependent
	myeloproliferative syndrome (2%-20%); cumulative dose and duration dependent
sexual/reproductive function	amenorrhea; typically duration dependent[5]
	infertility/sterility; testicular suppression, ovarian suppression/failure; reversible and irreversible
vascular	veno-occlusive disease; after high-dose melphalan

Adapted from standard reference[4] unless specified otherwise.

Hypersensitivity reactions including anaphylaxis have been reported in 2% of patients receiving melphalan. Hypersensitivity reactions occur most commonly after several courses of IV therapy[5,25]; early hypersensitivity reactions and reactions with oral melphalan have also been reported.[4,17] These reactions are characterized by urticaria, pruritis, edema, and in some patients tachycardia, bronchospasm, dyspnea, hypotension, chest pain, and rarely cardiac arrest.[4] Antihistamines and corticosteroids are standard treatment. Melphalan should be discontinued after a hypersensitivity reaction.[4]

Gastrointestinal toxicities: The nausea and vomiting, diarrhea, and stomatitis associated with melphalan are dose related.[8] Mild nausea and vomiting may occur in patients receiving conventional oral doses of melphalan[4,6,8,17]; however, routine prophylactic antiemetics are usually not required.[11,17] Administering melphalan in divided doses rather than as a single daily dose may reduce the incidence of nausea.[25] With high-dose IV therapy, vomiting, diarrhea, and stomatitis become the dose-limiting toxicities.[2-4]

Pulmonary fibrosis and interstitial pneumonitis have been reported with melphalan use.[4] Melphalan-related pulmonary toxicity is not related to dose or duration of therapy. Melphalan should be discontinued if signs of pulmonary toxicity occur (cough, fever, rales, dyspnea, respiratory distress, and hypoxia). A hypersensitivity mechanism may contribute to these toxicities.[1] Pulmonary fibrosis may be reversible following melphalan withdrawal and administration of steroids, but may progress despite withdrawal of melphalan.[1] Fatalities have occurred.[4]

Bone marrow suppression, primarily leukopenia and thrombocytopenia,[1] are the most common and dose-limiting side effects of melphalan.[4,5] Bone marrow suppression typically occurs gradually, is usually moderate in severity, and is reversible[4,5]; irreversible marrow failure has been reported.[4,5] With continuous short courses of therapy, leukopenia and thrombocytopenia typically do not occur until the second or third week of treatment and recover by 4-6 weeks.[2,3,5,26] Delayed myelosuppression may occur with counts continuing to fall for 6-8 weeks after initiation of therapy.[4] Rapid onset of profound myelosuppression often occurs at doses above 140 mg/m^2[2,3,26] Myeloma patients often do not have normal blood counts prior to melphalan treatment; abnormal blood counts may persist after discontinuing treatment. In these cases the nadir information will not be relevant. Due to the significant interpatient variability of oral melphalan absorption, it is recommended that the melphalan dosage be escalated until some myelosuppression is observed.[4] For patients with evidence of bone marrow failure, discontinue melphalan; evidence of marrow regeneration should be obtained before restarting treatment. The incidence of severe myelosuppression is greater in patients receiving IV melphalan.[5]

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Hyperuricemia may result from cell lysis by cytotoxic chemotherapy and may lead to electrolyte disturbances or acute renal failure.[27] It is most likely with highly proliferative tumours of massive burden, such as leukemias, high-grade lymphomas, and myeloproliferative diseases. The risk may be increased in patients with preexisting renal dysfunction, especially ureteral obstruction. Suggested prophylactic treatment for high-risk patients[28]:

- aggressive hydration
- allopurinol
- alkalinization of urine, if the uric acid level is elevated, use sodium bicarbonate IV or PO titrated to maintain urine pH > 7

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
carmustine[1,5,8,29]	increased risk of pulmonary toxicity	melphalan may reduce the threshold for carmustine-induced pulmonary toxicity	caution; monitor for pulmonary toxicity
cimetidine[5,26,30]	decreased therapeutic effect of oral melphalan	reduced bioavailability of oral melphalan by 30%; alteration of gastric acidity may decrease the absorption of melphalan; other mechanisms may be involved	usual monitoring[5]; no information found regarding a potential interaction between melphalan and other H_2-antagonists, antacids, or proton pump inhibitors
cyclosporine[4-6,29,31]	increased risk of nephrotoxicity	unknown	caution; monitor renal function; dose reduction of cyclosporine may be necessary when used with high-dose melphalan[5,29]
digoxin[6,31]	decreased effect of digoxin tablets	melphalan-induced changes on intestinal mucosa cause a 50% decrease in absorption of digoxin tablets within 24-48 h of melphalan initiation; absorption returns to normal within 1 week of melphalan discontinuation	consider monitoring digoxin levels, adjust digoxin dose as needed; digoxin oral elixir or liquid filled capsules may minimize the interaction due to rapid and extensive absorption of these formulations
interferon-alfa induced fever[5,29]	decreased therapeutic effect of melphalan	possible increased elimination via increased chemical reactivity of melphalan at the elevated temperature[2]; the increase in body temperature may increase the alkylating action of melphalan, countering the decreased melphalan serum concentrations[29]	usual monitoring[29]

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SUPPLY AND PREPARATION:

Tablets: Aspri Pharma Canada Inc. (for Aspen Pharma Trading Limited) supplies melphalan as a 2 mg film-coated tablet. Tablet does not contain lactose. Refrigerate.[32]

Injection: Aspri Pharma Canada Inc. (for Aspen Pharma Trading Limited) supplies melphalan hydrochloride as 50 mg vials of freeze-dried powder. A 10 mL vial of solvent-diluent is provided (buffer solution also contains ethanol and propylene glycol). Store at room temperature and protect from light.[32]

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.

Additional information: melphalan is incompatible with D5W and Lactated ringers[6,33]

PARENTERAL ADMINISTRATION:

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

Subcutaneous	not used due to corrosive nature
Intramuscular	not used due to corrosive nature
Direct intravenous	into tubing of running IV; see ***Systemic Therapy Policy III-20: Prevention and Management of Extravasation of Chemotherapy***
Intermittent infusion[5]	***over 15-20 minutes***; longer duration (up to 60 minutes) may be used when mixed in large volumes due to concentration-dependent stability requirements
Continuous infusion	not stable in solution
Intraperitoneal[1,5,25]	has been used
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial/Hyperthermic isolated limb perfusion[4,5]	has been used, see paragraph below
Intravesical	no information found

Hyperthermic isolated limb perfusion*:* Melphalan for injection has been administered by hyperthermic isolated limb perfusion, as an adjunct to surgery, for the local treatment of melanoma.[4] The recommended dose of melphalan for perfusion is 1.0 mg/kg for the upper extremity and 1.5 mg/kg for the lower extremity. The total dose for a melphalan perfusion should not exceed 80 mg for upper extremity and 120 mg for lower extremity. Melphalan is administered into the arterial line of the perfusion in 3 equally divided doses at 5-minute intervals. For further administration details please refer to the manufacturer's product monograph.[4] Melphalan concentrations decline rapidly from circulating perfusate with average terminal half-lives of 19 to 53 minutes.[4] Peak melphalan concentrations in the closed circuit perfusate are typically 10 to 100 times greater than peak concentrations in plasma observed following standard dose intravenous melphalan therapy.[4] Systemic exposure to melphalan during limb perfusion is generally very low.[4] Systemic complications are uncommon.
Side effects may include:

- edema and slight erythema (80%)[3]
- blistering (6%); typically occurs 14 days after treatment[3]
- wound complications, such as delayed healing and infection (5-10%)[4]

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- tissue necrosis and necrotizing fasciitis (<1%)[4,5]
- transient paralysis, limb pain, nerve injury, and peripheral neuritis[5]
- pulmonary embolism, severe nerve or muscle damage, and arterial or venous thrombosis requiring amputation (<1%)[4,5]
- reversible bone marrow suppression (<5%)[4]

Local toxicity increases with increasing dose, duration of perfusion, and temperature.[4]

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 absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

***Adults*:**

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

	Cycle Length:	
Oral:	***4 weeks*[11]*:***	***9 mg/m^2 PO once daily for four consecutive days starting on day 1*** (total dose per cycle 36 mg/m^2) adjusted to induce a therapeutic response but not cause a fall in neutrophil count below 1 x 10^9/L and/or a fall in platelet count below 100 x 10^9/L • round dose to the nearest 2 mg. • doses can be divided (e.g., BID-QID). • adjust dose according to hematologic response. • preferable to administer on an empty stomach. • several variations of the combination melphalan and prednisone regimen exist.[5,17]
	n/a[4]:	initial: 10 mg PO once daily for seven consecutive days (range 7-10 days) starting on day 1 (total dose 70 mg [range 70-100 mg]) followed by a rest period off treatment, during the drug free period monitor blood counts, once the white blood cell count is >4 x 10^9/L and the platelet count is >100 x 10^9/L, start maintenance therapy maintenance: 2 mg PO once daily adjusted to induce a therapeutic response but not cause a fall in neutrophil count below 3-3.5 x 10^9/L • preferable to administer on an empty stomach.

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

	Cycle Length:	
	n/a[4]:	initial: 6 mg PO once daily for fourteen consecutive days (range 14-21 days) starting on day 1, adjusted based on weekly blood counts (total dose 84 mg [range 84-126 mg]) followed by a rest period off treatment of up to 4 weeks, during the drug free period monitor blood counts, once the white blood cell count is >4 x 10^9/L and the platelet count is >100 x 10^9/L, start maintenance therapy maintenance: 2 mg PO once daily adjusted to induce a therapeutic response but not cause a fall in neutrophil count below 3-3.5 x 10^9/L • preferable to administer on an empty stomach.
	4-5 weeks[4]:	0.2 mg/kg PO once daily for five consecutive days starting on day 1 (total dose per cycle 1 mg/kg) • round dose to the nearest 2 mg. • preferable to administer on an empty stomach.
	n/a[4]:	initial: 0.15 mg/kg PO once daily for seven consecutive days starting on day 1 (total dose 1.05 mg/kg) followed by a rest period off treatment of 2-6 weeks, during the drug free period monitor blood counts, once the white blood cell and platelet count are rising, start maintenance therapy maintenance: 0.05 mg/kg PO once daily or 2 mg PO once daily adjusted to induce a therapeutic response but not cause a fall in counts below 3-3.5 x 10^9/L • round dose to the nearest 2 mg. • preferable to administer on an empty stomach.
Intravenous:	2-4 weeks[4]:	16 mg/m^2 IV for one dose on day 1 every two weeks for four cycles, then repeated every four weeks (total dose per cycle 16 mg/m^2) • adjusted on the basis of nadir blood counts.
	Bone marrow transplant[34]:	***200 mg/m^2 IV for one dose on day -1*** of Peripheral Blood Stem Cell Transplant (PBSCT) (total dose 200 mg/m^2) Note: these doses are fatal without BMT.
Perfusion Method:	see paragraph following **Parenteral Administration** table	

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

Concurrent radiation:

Cycle Length:
generally melphalan should not be used concurrently with radiation[4];
melphalan has been used with radiation when the benefits were believed to outweigh the risks

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:

dose reduction should be considered,[1,4] although melphalan is eliminated primarily by nonrenal mechanisms, patients with renal impairment are at risk for uremic marrow suppression[4]; numerous dosing guidelines exist:

- The manufacturer suggests a 50% dose reduction of the IV dose if BUN ≥ 11 mmol/L.

suggested dose adjustment for IV or PO[6,35]; not to be used for BMT dosing

Creatinine clearance* (mL/min)	Dose
>50	100%
10-50	75%
<10	50%

Calculated creatinine clearance = $\frac{N^* \times (140 - Age) \times weight\ (kg)}{Serum\ Creatinine\ in\ \mu mol/L}$

*For males N = 1.23; for females N=1.04

Dosage in hepatic failure:

no adjustment required[1]

Dosage in dialysis:

not removed from plasma to any significant degree by hemodialysis, hemoperfusion,[4] or peritoneal dialysis[1]

- Continuous arteriovenous hemofiltration (CAVH): administer 75% of usual dose[6,35]

Children:

safety and effectiveness in children not established[4]; melphalan has been used in pediatric patients[6,7,9]

Intravenous:

Cycle Length:
3-4 weeks[7,36]: 35 mg/m^2 (range 10-35 mg/m^2) IV for one dose on day 1 (total dose per cycle 35 mg/m^2 [range 10-35 mg/m^2])

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