

DRUG NAME: Melphalan

SYNONYM(S): L-PAM,¹ L-Sarcolysin,² Phenylalanine Mustard,¹⁻⁵ Phenylalanine Nitrogen Mustard²

COMMON TRADE NAME(S): ALKERAN®

CLASSIFICATION: alkylating agent⁴

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 N⁷ 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 ^{RW.ERRORRW.ERROR} 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 reference⁴ unless specified otherwise.

USES:

Primary uses:

- *Multiple myeloma
- *Ovarian cancer

Other uses:

- Breast cancer^{1,5}
- 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 macroglobulinemia¹

*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
- **Hepatitis B (HBV) reactivation:** All lymphoma patients should be tested for both HBsAg and HBcAb. If either test is positive, such patients should be treated with lamivudine 100 mg/day orally, for the entire duration of chemotherapy and for six months afterwards. Such patients should also be monitored with frequent liver function tests and HBV DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.¹¹

Carcinogenicity: Melphalan is carcinogenic.⁴

Mutagenicity: Mutagenic in Ames test and mammalian *in vitro* mutation test.^{12,13} 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.

Pregnancy: FDA Pregnancy Category D.⁶ There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., 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).

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.¹⁴ When placebo-controlled trials are available, adverse events are included if the incidence is \geq 5% higher in the treatment group.

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, ^{5,15} see paragraph following Side Effects table
	vasculitis
blood/bone marrow/ febrile neutropenia	anemia ⁵ (11-60%, severe 2-12%) ¹⁵ ; typically occurs 6-8 weeks after initiation of therapy; hemolytic anemia also reported
	immunosuppression, ¹ leukopenia, neutropenia (5-79%, severe 3-37%) ^{8,15} ; 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%), ^{8,15} 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 ¹⁴
dermatology/skin	extravasation hazard: vesicant ¹⁶
	alopecia (7-9%, severe 0.5%) ¹⁵ ; 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 ¹⁷ : dose related ; rare for low dose oral; highly emetogenic for high dose (≥ 100 mg/m²) and stem-cell or bone marrow transplantation ¹⁸⁻²²
	anorexia ⁷
	diarrhea; dose related, typically occurs 1 week after high-dose melphalan
	nausea and vomiting; dose related ⁵ ; ($\leq 30\%$, severe $< 2\%$) ^{6,8,15} ; (30-90% after high-dose melphalan) ^{6,21}
	stomatitis ($\leq 50\%$) ^{1,23} ; dose related ⁸
hemorrhage	hemorrhage ¹⁵ (severe 1-3%) ¹⁵
hepatobiliary/pancreas	hepatic toxicity; after high-dose melphalan ¹⁵
infection	infection not otherwise specified ¹⁵ (5-21%, severe 2-14%) ¹⁵
metabolic/laboratory	abnormal liver function tests; elevated transaminases ⁶ ; usually mild, typically seen with high-dose melphalan ¹⁵
	hyperuricemia; typically seen early after starting treatment in patients with renal damage

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	elevated serum creatinine
	hyponatremia ¹ ; after high-dose melphalan ¹
neurology	neuropathy ¹⁵ (2%) ¹⁵
	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 reference⁴ 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^{5,23}; early hypersensitivity reactions and reactions with oral melphalan have also been reported.^{4,15} 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^{4,6,8,15}; however, routine prophylactic antiemetics are usually not required.^{11,15} Administering melphalan in divided doses rather than as a single daily dose may reduce the incidence of nausea.²³ 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.^{2,3,5,24} 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^{2,3,24} 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

Hyperuricemia may result from cell lysis by cytotoxic chemotherapy and may lead to electrolyte disturbances or acute renal failure.²⁵ 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 patients²⁶:

- aggressive hydration
- allopurinol
- alkalization 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 ^{1,5,8,27}	increased risk of pulmonary toxicity	melphalan may reduce the threshold for carmustine-induced pulmonary toxicity	caution; monitor for pulmonary toxicity
cimetidine ^{5,24,28}	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 ^{4-6,27,29}	increased risk of nephrotoxicity	unknown	caution; monitor renal function; dose reduction of cyclosporine may be necessary when used with high-dose melphalan ^{5,27}
digoxin ^{6,29}	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

AGENT	EFFECT	MECHANISM	MANAGEMENT
interferon-alfa induced fever ^{5,27}	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 ²⁷	usual monitoring ²⁷

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.³⁰

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.³⁰

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^{6,31}

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 ^{RW.ERRORRW.ERROR} 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 ^{1,5,23}	has been used
Intrapleural	no information found
Intrathecal	no information found

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

<p>Cycle Length: n/aRW.ERRO RRW.ERROR⁴ :</p>	<p>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])</p> <p>followed by a rest period off treatment, during the drug free period monitor blood counts, once the white blood cell count is $>4 \times 10^9/L$ and the platelet count is $>100 \times 10^9/L$, start maintenance therapy</p> <p>maintenance: 2 mg PO once daily adjusted to induce a therapeutic response but not cause a fall in neutrophil count below $3-3.5 \times 10^9/L$</p> <ul style="list-style-type: none"> • Preferable to administer on an empty stomach.
<p>n/aRW.ERRO RRW.ERROR⁴ :</p>	<p>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])</p> <p>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 $>4 \times 10^9/L$ and the platelet count is $>100 \times 10^9/L$, start maintenance therapy</p> <p>maintenance: 2 mg PO once daily adjusted to induce a therapeutic response but not cause a fall in neutrophil count below $3-3.5 \times 10^9/L$</p> <ul style="list-style-type: none"> • Preferable to administer on an empty stomach.
<p>4-5 weeks⁴:</p>	<p>0.2 mg/kg PO once daily for five consecutive days starting on day 1 (total dose per cycle 1 mg/kg)</p> <ul style="list-style-type: none"> • Round dose to the nearest 2 mg. • Preferable to administer on an empty stomach.
<p>n/a⁴:</p>	<p>initial: 0.15 mg/kg PO once daily for seven consecutive days starting on day 1 (total dose 1.05 mg/kg)</p> <p>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</p> <p>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 $3-3.5 \times 10^9/L$</p> <ul style="list-style-type: none"> • Round dose to the nearest 2 mg. • Preferable to administer on an empty stomach.

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

<i>Intravenous:</i>	<p>Cycle Length: 2-4 weeks⁴: 16 mg/m² IV for one dose on day 1 every two weeks for four cycles, then repeated every four weeks (total dose per cycle 16 mg/m²)</p> <ul style="list-style-type: none"> Adjusted on the basis of nadir blood counts. <p><i>Bone marrow transplant</i>³²: 200 mg/m² IV for one dose on day -1 of Peripheral Blood Stem Cell Transplant (PBSCT) (total dose 200 mg/m²)</p> <p>Note: these doses are fatal without BMT.</p>								
<i>Perfusion Method:</i>	see paragraph following Parenteral Administration table								
<i>Concurrent radiation:</i>	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								
<i>Dosage in myelosuppression:</i>	modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"								
<i>Dosage in renal failure:</i>	<p>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 suppression⁴; numerous dosing guidelines exist:</p> <ul style="list-style-type: none"> The manufacturer suggests a 50% dose reduction of the IV dose if BUN \geq 11 mmol/L. <p>suggested dose adjustment for IV or PO^{6,33}; not to be used for BMT dosing</p> <table border="1"> <thead> <tr> <th>Creatinine clearance* (mL/min)</th> <th>Dose</th> </tr> </thead> <tbody> <tr> <td>>50</td> <td>100%</td> </tr> <tr> <td>10-50</td> <td>75%</td> </tr> <tr> <td><10</td> <td>50%</td> </tr> </tbody> </table> <p>Calculated creatinine clearance = $\frac{N^* \times (140 - \text{Age}) \times \text{weight (kg)}}{\text{Serum Creatinine in } \mu\text{mol/L}}$</p> <p>*For males N = 1.23; for females N=1.04</p>	Creatinine clearance* (mL/min)	Dose	>50	100%	10-50	75%	<10	50%
Creatinine clearance* (mL/min)	Dose								
>50	100%								
10-50	75%								
<10	50%								
<i>Dosage in hepatic failure:</i>	no adjustment required ¹								
<i>Dosage in dialysis:</i>	<p>not removed from plasma to any significant degree by hemodialysis, hemoperfusion,⁴ or peritoneal dialysis¹</p> <ul style="list-style-type: none"> Continuous arteriovenous hemofiltration (CAVH): administer 75% of usual dose^{6,33} 								
<u>Children:</u>	safety and effectiveness in children not established ⁴ ; melphalan has been used in pediatric patients ^{6,7,9}								
<i>Intravenous:</i>	<p>Cycle Length: 3-4 weeks^{7,34}: 35 mg/m² (range 10-35 mg/m²) IV for one dose on day 1 (total dose per cycle 35 mg/m² [range 10-35 mg/m²])</p>								

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