Drug Monograph

A - Drug Name

melphalan

COMMON TRADE NAME(S): Alkeran®

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B - Mechanism of Action and Pharmacokinetics

Melphalan is a phenylalanine derivative of mechlorethamine. Alkylation of DNA results in breaks in the DNA molecules as well as cross-linking of the twin strands, thus interfering with DNA replication and transcription of RNA. Like other alkylators, melphalan is cell cycle phase non-specific

Absorption	Oral: Incomplete, variable, 56-85% bioavailable post oral dose; food decreases AUC by 39-45%.	
Distribution	Rapid distribution into total body water. Pharmacokinetics are linear and similar in adults and children.	
	Cross blood brain barrier?	Limited; plasma to CNS ratio 10:1.
	PPB	55-60% serum albumin; some irreversible (20% α-acid glycoprotein)
Metabolism	Chemical hydrolysis to mono and dihydroxy products; primary means of elimination.	
	Active metabolites	No
	Inactive metabolites	Yes
Elimination	Biphasic; mainly feces; renal excretion low.	
	Feces	20-50% within 6 days (PO).

Urine	20-35% within 24 hours (PO); 10% as intact drug.
Half-life	(terminal) : 75 minutes (IV)

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C - Indications and Status

Health Canada Approvals:

- Malignant melanoma (hyperthermic isolated limb perfusion, as an adjuvant to surgery)
- Multiple myeloma
- Ovarian cancer (palliative)

Other Uses:

- Hodgkin's lymphoma
- Non-Hodgkin's lymphomas

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D - Adverse Effects

Emetogenic Potential: Moderate (IV)
Minimal – No routine prophylaxis; PRN recommended (PO)

Extravasation Potential: Vesicant

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Flushing (high doses)	I E
Dermatological	Alopecia (BMT doses)	E
	Rash	E
Gastrointestinal	Diarrhea (especially with high-dose regimens)	E
	Mucositis (with high doses)	E
	Nausea (or vomiting - PO: up to 30%; IV: up to 50%)	I
	Vomiting	I

General	Wound complication (reduced wound healing - limb perfusion)	I E
Hematological	Hemolysis	
	Myelosuppression	E
Hepatobiliary	Hepatitis	E
	Jaundice	E
	↑ LFTs	E
	Veno-occlusive disease	E
Hypersensitivity	Anaphylaxis (2%) (Type I anaphylactoid)	I
Injection site	Injection site reaction (50%) (transient; mild pain, irritation, warmth, tingling)	I
	Necrosis (rare; or ulceration)	I E
Metabolic / Endocrine	Hyperuricemia	
Musculoskeletal	↑CPK (with perfusion)	I
	Rhabdomyolysis (with perfusion)	I
Neoplastic	Leukemia (secondary)	L
	MDS	L
	Secondary malignancy	L
Renal	↑ BUN	E
	Creatinine increased	E
Reproductive and breast disorders	Infertility	L
	Irregular menstruation (amenorrhea)	D
Respiratory	Pneumonitis	E
	Pulmonary fibrosis (chronic, rare)	D
Vascular	Vasculitis	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most frequent dose-limiting toxicity is dose-related, cumulative myelosuppression.

Hypersensitivity reactions, including anaphylaxis, have been reported. Cardiac arrest has rarely been associated with such events. If a hypersensitivity reaction occurs, melphalan treatment should be discontinued.

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.

The **tissue necrosis** that occurs with **extravasation** may happen days to weeks after the treatment. Patients must be observed for delayed reactions and prior injection sites carefully inspected.

Nausea and vomiting occur rarely with chronic low-dose treatment, but may be more severe with single high oral or IV doses. With high dose therapy **gastrointestinal toxicity** (mucositis, esophagitis, and diarrhea) becomes dose-limiting.

Pulmonary fibrosis and interstitial pneumonitis have been reported. Signs and symptoms are dry cough, dyspnea, tachypnea, fever and cyanosis. Melphalan pulmonary toxicity is not related to dose or to duration of therapy. There are no identifiable risk factors. Patients either recover with complete resolution of all signs and symptoms of pulmonary toxicity or die from progressive pulmonary disease.

Alkylating agents cause **gonadal suppression**; therefore melphalan may cause amenorrhea or azoospermia, which may be irreversible. **Second malignancies** may occur in up to 20% of patients with prolonged exposure (over 600mg)

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E - Dosing

Refer to protocol by which patient is being treated. Numerous dosing schedules exist, depending 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:

Oral: 0.15 mg/kg daily x 7 days; 2-6 week break then ≤ 0.05mg/kg/day maintenance

Oral: 0.2 mg/kg Daily for 5 days; every 4-5 weeks

Oral: 6 mg daily x 2-3 weeks; 4 week break then 2 mg/day maintenance

Intravenous: 16 mg/m² (q2w x 4 doses, then q 4-week after recovery from toxicity)

Bone marrow transplant: Much higher doses are used for tumour ablation prior to marrow transplant than for standard treatment regimens.

Dosage with Toxicity:

- Discontinue if hypersensitivity or pneumonitis / pulmonary fibrosis occurs.

Dosage with myelosuppression:

- Do not retreat until platelets > 100 x 10^9/L and neutrophils > 1.5 x 10^9/L. Reduce melphalan after grade 4 neutropenia or grade 3 thrombocytopenia.
- Modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Hematologic and Non-Hematologic Toxicities."

Dosage with Hepatic Impairment:

No adjustment required.

Dosage with Renal Impairment:

Increased incidence of severe myelosuppression has been observed in patients with BUN ≥ 10.7 mmol/L. Dose reduction should be considered in patients with renal insufficiency receiving melphalan.

Creatinine clearance (mL/min)	% usual dose
10-50	75% and monitor
<10	50% and monitor

Dosage in the elderly:

No adjustment required, but caution should be exercised.

Children:

Safety and efficacy not established. Consult specific protocols for details.

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F - Administration Guidelines

IV MELPHALAN

- Slow push through sidearm of free-flowing IV (Normal Saline).
- For reconstitution, rapid addition of the supplied diluent to the drug vial followed by immediate vigorous shaking is important for proper dissolution.
- May dilute in Normal Saline to a concentration between 0.1 to 0.45 mg/mL; Infuse over 15-30 minutes.
- Should be administered within 50 minutes of reconstitution. Reconstituted product is stable for 2 hours at 30°C. Precipitate forms if refrigerated.

ORAL MELPHALAN

- Oral self-administration; drug available by outpatient prescription.
- Keep refrigerated.
- Take on an empty stomach.

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G - Special Precautions

Other:

Melphalan is contraindicated in patients whose disease has demonstrated a prior resistance to this agent, or have demonstrated hypersensitivity to melphalan or to any of its excipients. There is **cross-sensitivity** between melphalan and chlorambucil, which is manifested as a **rash**. Avoid the use of live vaccines.

Melphalan should be used with extreme caution in patients whose bone marrow reserve may have been compromised by prior radiation or chemotherapy, or whose marrow function is recovering from previous chemotherapy. Melphalan should not be administered concurrently with radiotherapy.

Melphalan is **carcinogenic**, **mutagenic** and **teratogenic**; it should not be used in **pregnancy**. Adequate contraception should be used by both sexes during melphalan treatment and for at least 6 months after treatment cessation. **Breast feeding** is not recommended due to the potential secretion into breast milk.

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Cimetidine (and H2 receptor antagonists)	↓ bioavailability of melphalan	Inhibit GI absorption	Monitor for ↓ melphalan activity
cyclosporine	↑ nephrotoxicity	Unknown	Monitor renal function
Nalidixic acid	↑ hemorrhagic enterocolitis	Unknown	Avoid concurrent treatment
Cisplatin	↑ melphalan levels and toxicity	↓ clearance	Caution
BCNU	↑ risk of interstitial pneumonitis	Unknown	Caution
Interferon	↓ levels of melphalan	↑ melphalan elimination	Caution

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I - 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

Monitor Type	Monitor Frequency
CBC	Baseline and regular
Clinical assessment for bleeding, infection, hematologic, pulmonary, GI, local toxicity.	At each visit

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

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Uric acid levels	Baseline and regular
Liver and renal function tests	Baseline and regular

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J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

- melphalan - oral tablets ()

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K - References

Cancer Drug Manual (the Manual), 1994, British Columbia Cancer Agency (BCCA)

McEvoy GK, editor. AHFS Drug Information 2009. Bethesda: American Society of Health-System Pharmacists, p. 1159-62.

Product Monograph: Alkeran® (melphalan). GlaxoSmithKline Inc., October 18, 2007.

June 2019 Updated emetic risk category.

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L - 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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