

DRUG NAME: Mechlorethamine**SYNONYM(S):** Chlormethine,^{1,2} HN₂,³ Mustine,³ Nitrogen Mustard³**COMMON TRADE NAME(S):** MUSTARGEN®**CLASSIFICATION:** alkylating agent,⁴ cytotoxic⁵*Special pediatric considerations are noted when applicable, otherwise adult provisions apply.***MECHANISM OF ACTION:**

Mechlorethamine, a bifunctional alkylating agent, interferes with DNA replication and RNA transcription as the result of formation of unstable carbonium ions which form interstrand cross-links with DNA,⁶ likely binding at the N⁷ position of guanine.^{7,8} Mechlorethamine has weak immunosuppressive properties.^{3,4} Mechlorethamine is cell cycle phase-nonspecific; however, its effect is most pronounced in the S phase, and cell proliferation is arrested in the G₂ phase.⁶

Topical activity of mechlorethamine may also involve immune mechanisms.⁹

Intracavitary (intra-pleural, -pericardial, and -peritoneal) administration of mechlorethamine produces an inflammatory reaction on serous membranes with a resulting sclerosing effect.^{3,10}

PHARMACOKINETICS:

Oral Absorption	not given orally due to irritation ³	
Distribution	not elucidated; rapid chemical transformation, combines with water or reactive cell compounds and is undetectable in the blood within minutes intracavitary: incomplete absorption, likely secondary to deactivation by body fluids ³	
	cross blood brain barrier?	no information found
	volume of distribution	no information found
	plasma protein binding	no information found
Metabolism	rapid hydrolysis by body fluids and demethylation in liver ⁶	
	active metabolite(s)	yes; ethylenimmonium derivative ^{1,10}
	inactive metabolite(s)	yes
Excretion	urine	<0.01% unchanged, ³ 50% as metabolite ⁶
	feces	<0.01% in bile ¹¹
	terminal half life	<1 min ⁶
	clearance	no information found

Adapted from standard reference⁴ unless specified otherwise.

USES:**Primary uses:**

- *Bronchogenic carcinoma
- *Leukemia, chronic lymphocytic
- *Leukemia, chronic myelogenous
- *Lymphoma, Hodgkin's
- *Lymphosarcoma
- *Malignant effusions (intracavitary)
- *Mycosis fungoides (IV)

*Health Canada approved indication

Other uses:

- Lymphoma, non-Hodgkin's¹⁰
- Mycosis fungoides (topical)^{3,12}

SPECIAL PRECAUTIONS:**Caution:**

- Mechlorethamine is a powerful vesicant.⁴
- Inhalation of mechlorethamine dust or vapors, or contact with skin or mucous membranes, especially the eyes, must be avoided.⁴ The preparation of injectable or topical mechlorethamine should be performed in a biological safety cabinet.⁴ Refer to product insert for further details on how to manage accidental contact with mechlorethamine, including the use of sodium thiosulfate.
- Mechlorethamine should not be used in patients with foci of acute or chronic suppurative inflammation as it may contribute to extensive and rapid development of amyloidosis.⁴
- Patients with chronic lymphocytic leukemia are especially sensitive to the myelosuppressive effects of mechlorethamine and should receive the drug with extreme caution, if at all.³

Carcinogenicity: Mechlorethamine is carcinogenic.⁴

Mutagenicity: Mutagenic in Ames test and mammalian *in vitro* mutation test.⁴ Mechlorethamine is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.⁴

Fertility: Both reversible and permanent sterility and infertility have been reported with mechlorethamine.^{4,6}

Pregnancy: FDA Pregnancy Category D.⁴ 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.¹³ When placebo-controlled trials are available, adverse events are included if the incidence is $\geq 5\%$ higher in the treatment group.

Table refers to IV dosing. For information regarding topical and intracavitary use, see paragraphs following Side Effects table.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
allergy/immunology	hypersensitivity reactions including anaphylaxis ($\leq 10\%$) ^{6,10}
auditory/hearing	ototoxicity ($>10\%$) ^{6,10} ; tinnitus ($\leq 10\%$) ⁶ and hearing loss ($<1\%$), dose-related ⁶
blood/bone marrow/ febrile neutropenia	decreased erythrocyte and hemoglobin levels; typically occurs 2 weeks after therapy, rarely significant
	hemolytic anemia ($<1\%$)
	lymphocytopenia, neutropenia ($>10\%$)⁶ ; typically occurs within 6-8 days and persists for 10-21 days
	pancytopenia; hematopoietic system may be suppressed >50 days after therapy
	thrombocytopenia ($>10\%$)⁶ ; typically occurs within 6-8 days and persists for 10-21 days
cardiovascular (general)	cardiotoxicity ¹ ; with high-dose ¹
constitutional symptoms	fatigue, drowsiness ³ (1-5%) ¹⁰ ; dose-related ¹⁰
	fever ³ ($\leq 10\%$) ^{3,6}

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in bold, italics	
	sweating ^{7,8}
dermatology/skin	<i>extravasation hazard: vesicant</i> ¹⁴
	alopecia ($\leq 10\%$) ^{6,10}
	erythema multiforme (<1%)
	facial angioedema ³
	rash; maculopapular, idiosyncratic, does not necessarily recur with rechallenge
gastrointestinal	<i>emetogenic potential: high</i> ¹⁵
	anorexia (1-10%) ^{6,10}
	diarrhea (1-10%) ^{6,10}
	mucositis, ¹⁶ stomatitis ¹⁰ ; typically occurs within 7-10 days with recovery in 10-14 days ¹¹
	<i>nausea and vomiting (~100%)⁶</i> ; typically occur 1-3 h after therapy, vomiting typically resolves in the first 8 hours; however, nausea may persist for 24 hours
	peptic ulcer ³ (<1%) ¹⁰
	metallic taste ³ ($\leq 10\%$) ^{3,6,10}
hemorrhage	hemorrhagic complications (<1%); hyperheparinemia has been reported
hepatobiliary/pancreas	hepatic dysfunction (<1%) ^{6,10}
infection	increased risk of infection; especially with concomitant corticosteroid use ³
metabolic/laboratory	elevated serum iron binding capacity ¹
	hyperuricemia (1-10%) ^{6,10}
neurology	confusion ¹⁰ (1-5%) ¹⁰ ; dose-related ^{10,17}
	dizziness (<1-10%) ⁶
	neurotoxicity ^{7,11} ; including convulsions, progressive muscle paralysis, cerebral degeneration, coma, and death ³ ; acute or delayed, with high-dose ^{3,7,11} or intra-arterial and regional perfusion ³
	paresthesia ³ (<1%) ¹⁰
	weakness (1-10%) ^{6,10}
ocular/visual	lacrimation ^{7,8}
pain	headache ³
	injection site pain ⁶
renal/genitourinary	renal function abnormalities
secondary malignancy	chromosomal abnormalities (>10%) ⁶
	secondary malignancies (1-6%) ⁶ ; including acute leukemia ¹
sexual/reproductive function	amenorrhea (20-85%) ^{6,11} ; temporary and permanent
	infertility/sterility; testicular suppression ($\leq 90\%$), ^{6,11} ovarian suppression/failure; reversible and permanent; spermatogenesis may return years after treatment
vascular	thrombosis; sclerosing thrombophlebitis (1-10%) ^{6,10} ; may progress to dark bluish-grey hyperpigmentation over several days, ³ avoid high concentration and prolonged local contact with the drug especially with elevated pressure in the antebrachial vein

Adapted from standard reference⁴ unless specified otherwise.

Local effects: Extravasation of mechlorethamine results in painful inflammation and induration. Sloughing may also occur.^{3,4} Administering mechlorethamine via a central venous catheter eliminates the risk of extravasation.¹⁸ For further information regarding the prevention and treatment of extravasation with mechlorethamine refer to BC Cancer Agency Provincial Systemic Therapy Program: [Prevention and Management of Extravasation of Chemotherapy](#).

Tumour lysis syndrome may result from cell lysis by cytotoxic chemotherapy and may lead to electrolyte disturbances or acute renal failure.¹⁹ 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 patients²⁰:

- aggressive hydration: 3 L/m²/24 hr with target urine output >100 mL/hr
- if possible, discontinuation of drugs that cause hyperuricemia (e.g., thiazide diuretics) or acidic urine (e.g., salicylates)
- monitoring of electrolytes, calcium, phosphate, renal function, LDH, and uric acid q6h for 24-48 hours
- electrolyte replacement as required
- allopurinol 600 mg po initially, then 300 mg po q6h for 6 doses, then 300 mg po daily for 5-7 days

Urine should be alkalinized only if the uric acid level is elevated, using sodium bicarbonate IV or PO titrated to maintain urine pH >7. Rasburicase (FASTURTEC®) is a novel uricolytic agent that catalyzes the oxidation of uric acid to a water-soluble metabolite, removing the need for alkalinization of the urine.²¹ It may be used for treatment or prophylaxis of hyperuricemia, 0.2 mg/kg IV daily for up to 7 days; however, its place in therapy has not yet been established.

Topical use: There is no evidence of any significant absorption of topical mechlorethamine.^{9,12,22} To minimize the risk of systemic exposure patients should be instructed to wash their hands after application of mechlorethamine and to avoid nail biting or finger licking. The emetogenic potential of topical mechlorethamine is unknown.¹⁵ Toxicities include:

- **allergic contact dermatitis** may occur in 50-67% of patients who use the aqueous solution.^{1,9,12,22} The potential for dermatitis is reduced to <25% when the ointment is used.^{9,12,22} This reaction is thought to represent a delayed cell-mediated allergic reaction^{1,9,23}; symptoms may appear days to months after initiating therapy.^{1,12} If contact dermatitis occurs, mechlorethamine should be discontinued. Depending upon the severity of the reaction, it may be treated with either systemic prednisone or topical glucocorticoids.⁹ Mechlorethamine therapy may be reinstated after a desensitization procedure. A reduced concentration of mechlorethamine is applied followed by a gradual increase in concentration over a period of months.⁹ Concurrent topical steroid may also be used during the desensitization procedure.²²
- **contact irritation or nonallergic dermatitis (10-25%)**^{9,12} Less frequent application or application of a reduced concentration may reduce irritation.^{9,24,25} Symptoms may also be managed with concomitant steroid application.⁹ These reactions are more common at skin folds or other sensitive skin areas such as the face.⁹
- **systemic allergic reactions (<1%)**¹² These include anaphylaxis, shortness of breath, and hives^{3,12} which typically occur minutes after application; however, allergic reactions have been reported after several doses.¹² If an immediate allergic reaction occurs, mechlorethamine therapy should not be restarted.¹²
- **hyperpigmentation**^{1,12,22,23} (>5%)¹²
- **dry skin** (>5%)^{12,22}; less frequent with ointment than with solution¹²
- **Stevens-Johnson syndrome** rare²²
- **non-melanoma epidermal cancer**^{1,9} The use of multiple sequential topical skin-damaging therapies and application of mechlorethamine to the genital skin areas may increase the risk.⁹

Intracavitary (intra-pleural, -pericardial, and -peritoneal) use produces unpredictable systemic effects.⁴ Systemic complications including nausea, vomiting, and myelosuppression occur less frequently with intracavitary use when

compared to IV^{3,4}; however, deaths have occurred following intracavitary use.⁴ Use caution when using intracavitary mechlorethamine concurrently with other agents which suppress the bone marrow.⁴ Pain occurs in <1% of patients with intrapleural use and in 1-10% with intraperitoneal use.⁴ Intracavitary use is often associated with mild nausea, vomiting, and diarrhea of 2-3 days duration.⁴ Hypovolemia has also been reported following intraperitoneal use.^{3,4} Transient cardiac arrhythmias may occur with intrapericardial use.⁴

INTERACTIONS:

No documented drug interactions.

SUPPLY AND STORAGE:

Injection: Ovation Pharmaceuticals supplies mechlorethamine as a 10 mg vial of mechlorethamine hydrochloride.⁴ Contains sodium chloride.³ Store at room temperature, protect from light and humidity.⁴

For basic information on the current brand used at the BC Cancer Agency, see [Chemotherapy Preparation and Stability Chart](#) in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at the BC Cancer Agency, see [Chemotherapy Preparation and Stability Chart](#) in Appendix.

Additional information: Mechlorethamine is unstable in neutral or alkaline solution. Although solutions prepared according to the manufacturers guidelines are acidic and decompose more slowly, the manufacturer recommends that they be prepared immediately before use.⁴

Compatibility of selected drugs: The following are compatible via Y-site injection: amifostine, aztreonam, filgrastim, fludarabine, granisetron, melphalan, ondansetron, sargramostim, teniposide, vinorelbine.^{6,26}

Incompatibility of selected drugs: The following are incompatible via Y-site injection: allopurinol, cefepime.^{6,26} The following is incompatible in the same infusion solution: methohexital.^{6,26}

PARENTERAL ADMINISTRATION:

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

Subcutaneous	not used due to corrosive nature
Intramuscular	not used due to corrosive nature
Direct intravenous	<i>Into tubing of running IV. Push slowly, so that drip of IV solution does not stop or reverse. Check for blood return before administration and after every 2-3 mL of drug. If no blood return, stop the injection and assess the IV site. Flush with 20 mL NS or D5W after administration to clear any remaining drug from tubing.</i> ^{3,4}
*Intermittent infusion	<i>has been used</i> ¹⁴
Continuous infusion	not stable in solution ⁴
Intracavitary	has been used ⁴ ; dilute in up to 100 mL NS ²⁶
Intrathecal	no information found

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

Intra-arterial	has been used ^{3,27}
Intravesical	no information found

*Administering mechlorethamine via a central venous catheter eliminates the risk of extravasation.¹⁸

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:

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

<i>Intravenous:</i>	Cycle Length: 3-6 weeks ^{3,4} :	0.4 mg/kg IV for one dose on day 1 (dose may be divided into two or four daily doses of 0.2 or 0.1 mg/kg respectively) (total dose per cycle 0.4 mg/kg)
		<ul style="list-style-type: none"> dosage should be based on ideal body weight, especially in the presence of edema or ascites repeat after hematologic recovery¹⁻³
	4 weeks ^{1,3,6} :	6 mg/m ² IV on day 1 (or days 1 and 8) (total dose per cycle 6 mg/m ² [range 6-12 mg/m ²])
<i>Intracavitary:</i>	n/a ^{1,3,4,6} :	0.4 mg/kg (range 0.2-0.4 mg/kg) or 10-20 mg intracavitary for one dose on day 1 (total dose 0.4 mg/kg [range 0.2-0.4 mg/kg])
		<ul style="list-style-type: none"> avoid concurrent systemic bone marrow depressants⁴
<i>*Topical:</i>		Apply to skin once a day (range 1-4 times daily) ^{9,12} until 12 months after a complete response is obtained. ^{9,12,25}
		<ul style="list-style-type: none"> treatment may be followed by maintenance treatments one to several times a week^{9,12}

Ointment^{2,3,9,12}: not commercially available.

- There is no official formula or compounding method.¹²
- Generally mechlorethamine is dissolved in dehydrated alcohol and the resulting solution is mixed in petrolatum or other anhydrous ointment base.
- Filtering the solution to remove insoluble sodium chloride is likely not necessary.
- Usual concentration: 0.01%.
- Lower concentrations can be used if hypersensitivity occurs.
- Higher concentrations (e.g., 0.02-0.04%) can be used for extensive or resistant lesions.
- Label: External use only.

Solution:^{3,9,12,22} has been used; not commercially available.

- Increased incidence of allergic contact dermatitis and less convenient than ointment.

*The preparation of topical mechlorethamine should be performed in a biological safety cabinet.⁴

Concurrent radiation: increased risk of myelosuppression with extensive radiation of bone marrow^{1,4}

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

<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>	no information found
<i>Dosage in hepatic failure:</i>	no information found
<i>Dosage in dialysis:</i>	hemodialysis: not removed ⁶ peritoneal dialysis: not removed ⁶

Children:

	safety and efficacy have not been established in children ⁴ ; mechlorethamine has been used in pediatric patients ^{4,8}
Intravenous:	Cycle Length: 4 weeks ^{8,16} : 6 mg/m ² (range 3-6 mg/m ²) IV on days 1 and 8 (total dose per cycle 12 mg/m ² [range 6-12 mg/m ²])
Topical:	has been used ⁹

REFERENCES:

1. DRUGDEX® Evaluations (database on the Internet). Mechlorethamine. Thomson MICROMEDEX®, 2007. Available from <http://www.micromedex.com/> Accessed 30 January 2007.
2. MARTINDALE- The Complete Drug Reference (database on the Internet). Chlormethine Hydrochloride. Thomson MICROMEDEX®, 2007. Available from <http://www.micromedex.com/> Accessed 30 January 2007.
3. McEvoy GK, editor. AHFS 2006 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc. p. 1127-9.
4. Ovation Pharmaceuticals Inc. MUSTARGEN® Package Insert. Deerfield, Illinois October 2005.
5. National Institute for Occupational Safety and Health (NIOSH). Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. Cincinnati, Ohio: NIOSH - Publications Dissemination; September 2004. p. 31-40.
6. Anonymous. Mechlorethamine. In: Rose BD, editor. UpToDate®. Waltham, Massachusetts: UpToDate 14.3; 2007.
7. Pizzo P, Poplack D. Principles and Practice of Pediatric Oncology. 5th ed. Philadelphia: Lippincott - Raven; 2006. p. 305-7.
8. Anonymous. Mechlorethamine: Pediatric drug information. In: Rose BD, editor. UpToDate®. Waltham, Massachusetts: UpToDate 14.3; 2007.
9. Kim YH, Kim YH. Management with topical nitrogen mustard in mycosis fungoides. Dermatol Ther 2003;16(4):288-98.
10. USPDI® Drug Information for the Health Care Professional (database on the Internet). Mechlorethamine (Systemic). Thompson MICROMEDEX®, 2007. Available from <http://www.micromedex.com/> Accessed 30 January 2007.
11. Solimando DA, Jr. Mechlorethamine and procarbazine. Hospital Pharmacy 1998;33(11).
12. USPDI® Drug Information for the Health Care Professional (database on the Internet). Mechlorethamine (Topical). Thompson MICROMEDEX®, 2007. Available from <http://www.micromedex.com/> Accessed 30 January 2007.
13. Joseph Connors, MD. Personal communication. Chair, BCCA Lymphoma Tumour Group; May 2006.
14. B.C. Cancer Agency Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and management of extravasation of chemotherapy. Vancouver, British Columbia: BC Cancer Agency; 1 September 2006.
15. BC Cancer Agency. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer Agency; 1 November 2005.
16. Pizzo P, Poplack D. Principles and Practice of Pediatric Oncology. 5th ed. Philadelphia: Lippincott - Raven; 2006. p. 300-3.
17. Wen PY, Plotkin SR. Neurologic complications of cancer chemotherapy. In: Rose BD, editor. UpToDate®. Waltham, Massachusetts: UpToDate 14.3; 2007.
18. Stephen Nantel, MD. Personal communication. BCCA Lymphoma Tumour Group; 29 March 2007.
19. DeVita VT, Hellman S, Rosenberg SA. Cancer Principles & Practice of Oncology. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 2640.
20. Leukemia/Bone Marrow Transplant Program of British Columbia. Leukemia/BMT Manual. 4th ed. Vancouver, British Columbia: Vancouver Hospital and Health Sciences Centre / BC Cancer Agency; 2003. p. 27.
21. Sanofi-Synthelabo. Rasburicase product information package. Markham, Ontario; 2004.
22. Smith BD, Wilson LD, Smith BD, et al. Management of mycosis fungoides: Part 2. Treatment.[see comment]. Oncology (Huntington) 1433;17(10):1419-28; discussion 30.

23. Selkin BA, Savarese DM. Cutaneous complications of chemotherapy. In: Rose BD, editor. UpToDate®. Waltham, Massachusetts: UpToDate 14.3; 2007.
24. Esteve E, Bagot M, Joly P, et al. A Prospective Study of Cutaneous Intolerance to Topical Mechlorethamine Therapy in Patients With Cutaneous T-Cell Lymphomas. *Arch Dermatol* 1999;135(11):1349-53.
25. Christina Parsons, MD. Personal communication. *BCCA Radiation Oncologist*;27 February 2007.
26. Trissel L. Handbook on injectable drugs. 13th ed. Bethesda, Maryland: American Society of Health-System Pharmacists; 2005. p. 954-5.
27. Shiu MH, Knapper WH, Fortner JG, et al. Regional isolated limb perfusion of melanoma intransit metastases using mechlorethamine (nitrogen mustard). *J Clin Oncol* 1986;4(12):1819-26.