DRUG NAME: Mechlorethamine

SYNONYM(S): Chlormethine,\(^1,2\) HN₂,\(^3\) Mustine,\(^3\) Nitrogen Mustard\(^3\)

COMMON TRADE NAME(S): MUSTARGEN®

CLASSIFICATION: alkylating agent,\(^4\) cytotoxic\(^5\)

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 N\(^7\) 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:

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

Adapted from standard reference\(^4\) 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’s\(^10\)
Mycosis fungoides (topical)\(^3,12\)
SPECIAL PRECAUTIONS:

Caution:
- Mechlorethamine is a powerful vesicant. The preparation of injectable or topical mechlorethamine should be performed in a biological safety cabinet. 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.
- 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.

Carcinogenicity: Mechlorethamine is carcinogenic.

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

Fertility: Both reversible and permanent sterility and infertility have been reported with mechlorethamine.

Pregnancy: FDA Pregnancy Category D. 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.

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 are included if the incidence is >5% higher in the treatment group.

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

<table>
<thead>
<tr>
<th>ORGAN SITE</th>
<th>SIDE EFFECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>allergy/immunology</td>
<td>hypersensitivity reactions including anaphylaxis (&lt;10%)&lt;sup&gt;6,10&lt;/sup&gt;</td>
</tr>
<tr>
<td>auditory/hearing</td>
<td>ototoxicity (&gt;10%)&lt;sup&gt;6,10&lt;/sup&gt;, tinnitus (&lt;10%)&lt;sup&gt;6&lt;/sup&gt; and hearing loss (&lt;1%), dose-related&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>blood/bone marrow/febrile neutropenia</td>
<td>decreased erythrocyte and hemoglobin levels; typically occurs 2 weeks after therapy, rarely significant</td>
</tr>
<tr>
<td></td>
<td>hemolytic anemia (&lt;1%)</td>
</tr>
<tr>
<td></td>
<td>lymphocytopenia, neutropenia (&gt;10%)&lt;sup&gt;6&lt;/sup&gt;; typically occurs within 6-8 days and persists for 10-21 days</td>
</tr>
<tr>
<td></td>
<td>pancytopenia; hematopoietic system may be suppressed &gt;50 days after therapy</td>
</tr>
<tr>
<td></td>
<td>thrombocytopenia (&gt;10%)&lt;sup&gt;6&lt;/sup&gt;; typically occurs within 6-8 days and persists for 10-21 days</td>
</tr>
<tr>
<td>cardiovascular (general)</td>
<td>cardiotoxicity&lt;sup&gt;1&lt;/sup&gt;; with high-dose&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>constitutional symptoms</td>
<td>fatigue, drowsiness&lt;sup&gt;2&lt;/sup&gt; (1-5%)&lt;sup&gt;10&lt;/sup&gt;; dose-related&lt;sup&gt;10&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>fever&lt;sup&gt;2&lt;/sup&gt; (&lt;10%)&lt;sup&gt;3,6&lt;/sup&gt;</td>
</tr>
<tr>
<td>ORGAN SITE</td>
<td>SIDE EFFECT</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>dermatology/skin</td>
<td>sweating, extravasation hazard: vesicant, alopecia (&lt;10%), erythema multiforme (&lt;1%), facial angioedema, rash; maculopapular, idiosyncratic, does not necessarily recur with rechallenge</td>
</tr>
<tr>
<td>gastrointestinal</td>
<td>emetogenic potential: high, anorexia (1-10%), diarrhea (1-10%), mucositis, stomatitis, typically occurs within 7-10 days with recovery in 10-14 days</td>
</tr>
<tr>
<td>hemorrhage</td>
<td>hemorrhagic complications (&lt;1%); hyperheparinemia has been reported</td>
</tr>
<tr>
<td>hepatobiliary/pancreas</td>
<td>hepatic dysfunction (&lt;1%)</td>
</tr>
<tr>
<td>infection</td>
<td>increased risk of infection; especially with concomitant corticosteroid use</td>
</tr>
<tr>
<td>metabolic/laboratory</td>
<td>elevated serum iron binding capacity, hyperuricemia (1-10%)</td>
</tr>
<tr>
<td>neurology</td>
<td>confusion (1-5%), dose-related, dizziness (&lt;1-10%), neurotoxicity, including convulsions, progressive muscle paralysis, cerebral degeneration, coma, and death; acute or delayed, with high-dose or intra-arterial and regional perfusion</td>
</tr>
<tr>
<td>ocular/visual</td>
<td>lacrimation</td>
</tr>
<tr>
<td>pain</td>
<td>headache</td>
</tr>
<tr>
<td>renal/genitourinary</td>
<td>renal function abnormalities</td>
</tr>
<tr>
<td>secondary malignancy</td>
<td>chromosomal abnormalities (&gt;10%)</td>
</tr>
<tr>
<td>sexual/reproductive function</td>
<td>amenorrhea (20-85%), temporary and permanent, infertility/sterility; testicular suppression (&lt;90%); reversible and permanent; spermatogenesis may return years after treatment</td>
</tr>
<tr>
<td>vascular</td>
<td>thrombosis; sclerosing thrombophlebitis (1-10%); may progress to dark bluish-grey hyperpigmentation over several days; avoid high concentration and prolonged local contact with the drug especially with elevated pressure in the antecubital vein</td>
</tr>
</tbody>
</table>

Adapted from standard reference unless specified otherwise.
Local effects: Extravasation of mechlorethamine results in painful inflammation and induration. Sloughing may also occur.\textsuperscript{3,4} Administering mechlorethamine via a central venous catheter eliminates the risk of extravasation.\textsuperscript{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.\textsuperscript{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 patients:\textsuperscript{20}

- aggressive hydration: 3 L/m\textsuperscript{2}/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\textsuperscript{®}) 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{15} Toxicities include:

- allergic contact dermatitis may occur in 50-67% of patients who use the aqueous solution.\textsuperscript{1,9,12,22} The potential for dermatitis is reduced to <25% when the ointment is used.\textsuperscript{9,12,22} This reaction is thought to represent a delayed cell-mediated allergic reaction;\textsuperscript{1,9,23} symptoms may appear days to months after initiating therapy.\textsuperscript{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.\textsuperscript{9} Mechlorethamine therapy may be reinitiated after a desensitization procedure. A reduced concentration of mechlorethamine is applied followed by a gradual increase in concentration over a period of months.\textsuperscript{9} Concurrent topical steroid may also be used during the desensitization procedure.\textsuperscript{22}

- contact irritation or nonallergic dermatitis (10-25%)\textsuperscript{9,12} Less frequent application or application of a reduced concentration may reduce irritation.\textsuperscript{9,24,25} Symptoms may also be managed with concomitant steroid application.\textsuperscript{9} These reactions are more common at skin folds or other sensitive skin areas such as the face.\textsuperscript{9}

- systemic allergic reactions (<1%)\textsuperscript{12} These include anaphylaxis, shortness of breath, and hives\textsuperscript{3,12} which typically occur minutes after application; however, allergic reactions have been reported after several doses.\textsuperscript{12} If an immediate allergic reaction occurs, mechlorethamine therapy should not be restarted.\textsuperscript{12}

- hyperpigmentation\textsuperscript{1,12,22,23} (>5%)\textsuperscript{12}

- dry skin (>5%)\textsuperscript{12,22}; less frequent with ointment than with solution\textsuperscript{12}

- Stevens-Johnson syndrome rare\textsuperscript{22}

- non-melanoma epidermal cancer\textsuperscript{1,9} The use of multiple sequential topical skin-damaging therapies and application of mechlorethamine to the genital skin areas may increase the risk.\textsuperscript{9}

Intracavitary (intra-pleural, -pericardial, and -peritoneal) use produces unpredictable systemic effects.\textsuperscript{4} Systemic complications including nausea, vomiting, and myelosuppression occur less frequently with intracavitary use when...
Mechlorethamine compared to IV\textsuperscript{3,4}; however, deaths have occurred following intracavitary use.\textsuperscript{4} Use caution when using intracavitary mechlorethamine concurrently with other agents which suppress the bone marrow.\textsuperscript{4} Pain occurs in <1\% of patients with intrapleural use and in 1-10\% with intraperitoneal use.\textsuperscript{4} Intracavitary use is often associated with mild nausea, vomiting, and diarrhea of 2-3 days duration.\textsuperscript{3,4} Hypovolemia has also been reported following intraperitoneal use.\textsuperscript{3,4} Transient cardiac arrhythmias may occur with intrapericardial use.\textsuperscript{4}

**INTERACTIONS:**

No documented drug interactions.

**SUPPLY AND STORAGE:**

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

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

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

**PARENTERAL ADMINISTRATION:**

<table>
<thead>
<tr>
<th>Method</th>
<th>BCCA administration guideline noted in bold, italics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous</td>
<td>not used due to corrosive nature</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>not used due to corrosive nature</td>
</tr>
</tbody>
</table>
| Direct intravenous | *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.*\textsuperscript{3,4}
| *Intermittent infusion* | *has been used*\textsuperscript{14} |
| Continuous infusion | not stable in solution\textsuperscript{6} |
| Intracavitary   | has been used\textsuperscript{6}; dilute in up to 100 mL NS\textsuperscript{26} |
| Intrathecal     | no information found                                 |

BC Cancer Agency Cancer Drug Manual\textsuperscript{6} Page 5 of 8 Mechlorethamine
Developed: September 1994
Revised: 1 May 2007
Intra-arterial has been used\(^3\,27\), italics
Intravesical no information found

*Administering mechlorethamine via a central venous catheter eliminates the risk of extravasation.\(^1\,8\)

**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:**

<table>
<thead>
<tr>
<th>Administration Method</th>
<th>Cycle Length</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>3-6 weeks(^{3,4})</td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td>4 weeks(^{1,3,6})</td>
<td>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)])</td>
</tr>
<tr>
<td>Intracavitary</td>
<td>n/a(^{1,3,4,6})</td>
<td>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])</td>
</tr>
<tr>
<td></td>
<td></td>
<td>avoid concurrent systemic bone marrow depressants(^4)</td>
</tr>
</tbody>
</table>

**Topical:**

Apply to skin once a day (range 1-4 times daily)\(^9\,12\) until 12 months after a complete response is obtained.\(^9\,12\,25\)

- treatment may be followed by maintenance treatments one to several times a week\(^9\,12\)

**Ointment**\(^2\,3\,9\,12\) has been used; 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\(^1\,4\)
Mechlorethamine

BCCA usual dose noted in bold, italics

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 “Dosage Modification for Myelosuppression”

Dosage in renal failure: no information found

Dosage in hepatic failure: no information found

Dosage in dialysis: hemodialysis: not removed; peritoneal dialysis: not removed

Children: safety and efficacy have not been established in children; mechlorethamine has been used in pediatric patients

Cycle Length:

Intravenous: 4 weeks; 6 mg/m² (range 3-6 mg/m²) IV on days 1 and 8 (total dose per cycle 12 mg/m² [range 6-12 mg/m²])

Topical: has been used

REFERENCES: