Drug Monograph

A - Drug Name

chlorambucil

COMMON TRADE NAME(S): Leukeran®

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B - Mechanism of Action and Pharmacokinetics

Chlorambucil was synthesized in 1953. It is an aromatic derivative of mechlorethamine, is closely related in structure to melphalan and is a bifunctional alkylating agent. DNA alkylation by the reactive ethylenimonium radical results in breaks in the DNA molecule as well as cross-linking of the twin strands, thus interfering with DNA replication and transcription of RNA. Like other alkylators, chlorambucil is cell cycle phase-nonspecific. The immunosuppressive activity of chlorambucil is due to its suppression of lymphocytes.

Absorption	Bioavailability	oral: Yes, bioavailability 70-80%. Food decreases bioavailability by 10-20%.
Distribution	Rapidly cleared from plasma; tissue distribution fairly homogeneous; crosses placenta; found in ascitic fluid.	
	Cross blood brain barrier?	no information found, but can cause seizures in high doses.
	Volume of distribution	0.14-0.24 L/kg
	PPB	99% (albumin)
Metabolism	Extensively metabolized in liver by the hepatic microsomal enzyme oxidation system	
	Active metabolites	phenylacetic acid mustard.

	Inactive metabolites	Yes
Elimination	Extremely low urinary excretion. Chlorambucil and its metabolites are probably not dialysable.	
	Urine	15-60% in 24 hours; less than 1% as intact drug / active metabolite.
	Half-life	1.5 hours

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C - Indications and Status

Health Canada Approvals:

- Monotherapy in chronic lymphocytic leukemia
- Monotherapy or combination therapy in:
  - Non-Hodgkin's lymphoma (e.g. follicular, MALT, mantle cell lymphoma, Waldenstrom's macroglobulinemia)
  - Hodgkin's lymphoma (palliative)

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

Extravasation Potential: Not applicable

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Dermatological	Rash (may be severe)	E
Gastrointestinal	Diarrhea (infrequent)	I
	Mucositis (infrequent)	E
	Nausea, vomiting (infrequent)	I
Hematological	Immunosuppression	E
	Myelosuppression ± infection, bleeding (may be	E

	severe)	
Hepatobiliary	Hepatotoxicity	D
Hypersensitivity	Drug reaction	I
Metabolic / Endocrine	Tumour lysis syndrome	I
Neoplastic	Leukemia (secondary) (or other malignancies)	L
Nervous System	Neurotoxicity	E
	Peripheral neuropathy	L
	Seizure (Rare, with high doses, prior history)	E
Reproductive and breast disorders	Infertility	L
Respiratory	Pneumonitis	E
Urinary	Cystitis (sterile)	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)

Myelosuppression is more severe following continuous administration than intermittent high dose chlorambucil and is dose-related. Prolonged therapy or excessive doses may result in pancytopenia or irreversible bone marrow damage.

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.

Pulmonary toxicity similar to other alkylating agents can occur, including interstitial pulmonary fibrosis or pneumonitis. Signs and symptoms are dyspnea, dry cough, fever, rales and tachypnea developing over a 1-2 month period. It is usually associated with prolonged therapy (6-24 months) and related to a total dose of >2 g. Partial recovery can occur within several weeks after discontinuing therapy and administration of steroids. In other patients, pulmonary complications progress and some deaths have occurred.

Children with nephrotic syndrome and patients receiving high pulse doses or with a prior history of seizures may have an increased risk of ***seizures***, and should be closely monitored. Rare, focal and/or generalized seizures have also occurred in patients receiving therapeutic daily doses.

Rarely, ***skin rash*** may occur and result in Stevens-Johnson Syndrome, toxic epidermal necrolysis or erythema multiforme. Chlorambucil should be discontinued immediately if skin reactions occur. Patients with a history of rash with other alkylating agents may have an increased risk of rash.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

CLL patients with pancytopenia should receive prednisone initially, and chlorambucil should only be started with some evidence of recovery – the initial dose of chlorambucil when started should not exceed 0.1 mg/kg/day.

Adults:

Continuous regimens:

- Induction: 0.1-0.2 mg/kg/day PO (CLL - until white cell count 10 x 10^9/L; for 4-8 weeks for NHL)
- Maintenance: After 4-week “rest”: 0.03-0.1 mg/kg/day PO adjusted to tolerance

Intermittent regimens:

- q28d: 6 mg/m^2/d PO for 7-14 days

Dosage with Toxicity:

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."

Toxicity and grade	Action	Dose when restart
Severe myelosuppression/ bone marrow failure	Discontinue	N/A
Grade 3 hematologic	Hold*	↓ by 33%
Grade 4 hematologic, febrile neutropenia or thrombocytopenic bleeding	Hold*	↓ by 33% or Discontinue

Grade 3 non-hematologic	Hold*	↓ by 33%
Skin or pulmonary toxicity or Grade 4 non-hematologic	Discontinue	N/A

*Before retreatment, major organ toxicities should recover to ≤ Grade 2, platelets ≥ 100 x 10^9/L, and ANC ≥ 1.5 x 10^9/L.

Dosage with Hepatic Impairment:

Adjustment required with severe hepatic impairment; no details found.

Dosage with Renal Impairment:

No adjustment required, but monitor carefully as at increased risk of myelosuppression.

The following dosage adjustments have been used by some clinicians:

Creatinine Clearance (mL/min)	**% Dose**
10-50	75%
<10	50%

Dosage in the elderly:

No overall differences in safety or effectiveness were observed between younger patients and patients ≥ 65 years. Use with caution due to possible decreases in hepatic, renal, or cardiac function.

Children:

Safety and efficacy have not been established.

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F - Administration Guidelines

- Oral self-administration; drug available by outpatient prescription.
- Keep drug refrigerated; do not freeze

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G - Special Precautions

Other:

Chlorambucil is **contraindicated** in patients who are resistant to the drug or who have developed hypersensitivity to it; there may be cross-sensitivity with other alkylating agents (especially rash) .

Should not be used within 4 weeks of a full course of radiation therapy or chemotherapy. **Administer with caution** if bone marrow is severely depressed and in patients with seizure disorders. Avoid live vaccines.

Chlorambucil has been shown to have **teratogenic**, **mutagenic** and **carcinogenic** properties in experimental models and should not be used in **pregnancy**. Adequate contraception must be used by patients and their partners, during treatment and for at least 6 months after chlorambucil cessation (general recommendation). Chlorambucil is known to cross the placenta. **Breast feeding** is not recommended because of the potential secretion of chlorambucil into breast milk. Secondary malignancies have been reported.

Both reversible and permanent **sterility** have been observed in patients. Children receiving chlorambucil before puberty generally have a normal progression of puberty. In males, however, testicular atrophy may occur and persist.

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Phenylbutazone	↑ the toxicity of chlorambucil	Unknown	Modify chlorambucil doses
Succinylcholine	prolonged apnea	inhibition of serum cholinesterase	decrease dose of succinylcholine
Live vaccines	systemic viral infection risk	immunosuppression	avoid / 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.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Weekly or twice weekly
Toxicity assessment (seizures, GI, hypersensitivity, TLS, infection, bleeding, pulmonary)	Routinely

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

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests	Periodic

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J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

- chlorambucil ()

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K - References

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Product Monograph: Leukeran® (chlorambucil). Triton Pharma Inc. Canada, November 29, 2010.

Product Monograph: Leukeran® (chlorambucil). GlaxoSmithKline Inc. USA, October 2011.

November 2024 Updated Pregnancy and Lactation section

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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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