DRUG NAME: Chlorambucil

SYNONYM(S): Chlorambucilum,[1] Chloraminophene,[2] Chlorbutinum,[1] CB-1348,[1], NSC-3088[1]

COMMON TRADE NAME(S): LEUKERAN®

CLASSIFICATION: alkylating agent

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Chlorambucil is a derivative of nitrogen mustard and acts as a cell cycle phase-nonspecific bifunctional alkylating agent.[3,4] Alkylation takes place through the formation of a highly reactive ethylenimonium radical.[3] This radical likely forms a cross-linkage between two strands of DNA, interfering with DNA, RNA and protein synthesis.[3,5] Chlorambucil also demonstrates immunosuppressive activity principally due to its suppression of lymphocytes.[5]

PHARMACOKINETICS:

Oral Absorption	70-80%,[2] rapidly and completely absorbed,[5] bioavailability reduced by 10-20% with food[6]	
Distribution	to liver, ascitic fluid, fat, crosses the placenta[7]	
	cross blood brain barrier?	no information found
	volume of distribution[6]	0.14-0.24 L/kg
	plasma protein binding	99%
Metabolism	primarily hepatic	
	active metabolite(s)	phenylacetic acid mustard
	inactive metabolite(s)	monohydroxy and dihydroxy derivatives
Excretion	urine	low urinary excretion, as almost completely metabolized
	feces	no information found
	terminal half life[3,5,6]	1.5 h; 1.8-2.5 h phenylacetic acid mustard
	clearance[8]	0.16 ± 0.04 L/hr/kg

Adapted from standard reference[3] unless specified otherwise.

USES:

Primary uses:
*Chronic lymphocytic leukemia
*Hodgkin's lymphoma
*Non-Hodgkin's lymphoma

*Health Canada approved indication

Other uses:
Gestational trophoblastic tumour[6]
Ovarian cancer[2,4,6]

SPECIAL PRECAUTIONS:

Caution:

- Patients with a history of skin rash with other alkylating agents may have increased risk of rash with chlorambucil.[3]
- Chlorambucil should not be used within four weeks of a full course of radiation or chemotherapy[3]; chlorambucil has been used with radiation when the benefits were believed to outweigh the risks,[5] a dose reduction may be considered.[4,9]

Carcinogenicity: Chlorambucil is carcinogenic.[3]

Mutagenicity: Mutagenic in Ames test.[10] Chlorambucil is clastogenic in mammalian *in vitro* chromosome tests.[3,11]

Fertility: Chlorambucil therapy may result in impairment of fertility; suppression of ovarian function, amenorrhea and azoospermia have been reported.[3] Varying degrees of recovery of spermatogenesis have occurred.[3]

Pregnancy: FDA Pregnancy Category D.[2,5] 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.[3]

Special populations: Patients with ***impaired renal function*** are prone to additional myelosuppression associated with azotemia.[3] Chlorambucil is ***epileptogenic***; patients with a history of seizures or head trauma, children with nephrotic syndrome, or patients receiving other potentially epileptogenic drugs should be closely monitored.[3] When ***lymphatic infiltration*** of the bone marrow is present, or the bone marrow is ***hypoplastic***, the daily dose should not exceed 0.1 mg/kg.[3] Chlorambucil is unsafe in patients with ***porphyria***.[1]

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.[9] When placebo-controlled trials are available, adverse events are included if the incidence is ≥ 5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology	***allergic cutaneous reactions; have occurred following initial or subsequent dosing***[5]
	angioedema; has occurred following initial or subsequent dosing[5]
blood/bone marrow/ febrile neutropenia	anemia,[5] ***hemolytic anemia***[12]
	immunosuppression, leukopenia, neutropenia, lymphopenia (>5%)[4]***; nadir after a single high dose days 7-14, recovery by 2-3 weeks***[5]
	pancytopenia; with prolonged therapy
	thrombocytopenia (>5%)[4]***; nadir after a single high dose days 7-14, recovery by 2-3 weeks***[5]
constitutional symptoms	fatigue[5]
	fever[13] (<1%)[4]
dermatology/skin	alopecia; (<1%)[5]
	pruritis[5]
	rash (≤5%)[4]
	Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis (<1%)[4]; has occurred following initial or subsequent dosing with chlorambucil[2,5]
	urticaria; has occurred following initial or subsequent dosing[5]
endocrine	ADH secretion abnormality; SIADH[6]
gastrointestinal	*emetogenic potential:rare*[14]*;* associated with single oral doses of 20 mg or more[4]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	anorexia; with doses ≥ 20 mg[5]
	mucositis (≤5%)[4]
	diarrhea (<1%); with doses ≥ 20 mg[5]
	nausea and vomiting; usually lasts less than 24 hours, and becomes less frequent with continued therapy, may persist up to 7 days after a single high dose[4]
hepatobiliary/pancreas	hepatotoxicity (<1%)[4]
infection	interstitial pneumonia
lymphatics	allergic lymphadenopathy[13]
metabolic/laboratory	asymptomatic increases in liver enzymes; alkaline phosphatase and AST[5]
	hyperuricemia[5] (≤5%)[4]; generally occurs shortly after starting treatment[4]
neurology	agitation[5] (<1%)[4]
	ataxia[5]
	confusion[5] (<1%)[4]
	hallucinations[5] (<1%)[4]
	motor neuropathy (<1%)[4]; flaccid paralysis[5]
	myoclonia (<1%)[4]
	peripheral neuropathy
	seizures (<1%)[4]; focal and/or generalized, generally occurs days to months after initiating treatment [4]
	tremor
ocular/visual	optic atrophy; (<1%) generally occurs after long-term use[1]
pain	abdominal pain; incidence increases with doses ≥ 20 mg[5,9]
pulmonary	interstitial pulmonary fibrosis (<1%)[4]; generally occurs after long-term use[4,15]
	pneumonitis[2]
renal/genitourinary	cystitis; generally occurs after long-term use[1]
secondary malignancy	leukemia; generally occurs after long-term use[3]
	solid tumours[5]
sexual/reproductive function	infertility/sterility
	amenorrhea[5]

Adapted from standard reference[3] unless specified otherwise.

Bone marrow suppression, the most common side effect of chlorambucil, generally occurs gradually, is usually moderate in severity and is reversible.[3,5] After a single high dose of chlorambucil, the leukocyte and platelet nadir occur 7-14 days after treatment and recover in 2-3 weeks.[5] With continuous short courses of therapy, leukopenia and thrombocytopenia typically do not occur until the third week of treatment and persist for 1-2 weeks after chlorambucil is discontinued, though 3-4 weeks have been reported.[5] The neutrophil count may decrease for up to 10 days after the last dose.[4,5]Leukemia patients often do not have normal blood counts prior to chlorambucil treatment; abnormal blood counts may persist after discontinuing treatment. In these cases the nadir information will not be relevant.[9]

With higher doses and prolonged therapy, cumulative dose approaching 6.5 mg/kg, the risk of causing irreversible bone marrow suppression increases[3]; it is believed that total chlorambucil dosage may not clearly predict bone marrow suppression and may occur at lower cumulative dosages.[5] Short intermittent courses may cause less risk of serious bone marrow depression than continuous therapy, by allowing bone marrow regeneration between courses.[4,5] For patients with evidence of bone marrow failure, discontinue chlorambucil; evidence of marrow regeneration should be obtained before restarting treatment.[3]

Skin rash occasionally occurs; hypersensitivity reactions, including rash progressing to Stevens-Johnson syndrome, erythema multiforme, or toxic epidermal necrolysis have been reported.[3] Patients with a history of skin rash with other alkylating agents may have increased risk of rash with chlorambucil.[3] Chlorambucil should be promptly discontinued in patients who develop skin reactions.[3]

Pulmonary fibrosis and interstitial pneumonia have occurred following intermittent or prolonged continuous dosing of chlorambucil.[5] Chlorambucil should be discontinued if signs of pulmonary toxicity occur (cough, fever, rales, dyspnea, respiratory distress, and hypoxia). Pulmonary fibrosis may be reversible following chlorambucil withdrawal[3]and administration of steroids[5]; pulmonary complications may progress despite withdrawal of chlorambucil and deaths have occurred.[5]

Fertility: Both reversible and permanent sterility and infertility have been reported with chlorambucil. [3,5] These effects appear to be related to dose and length of therapy[4,5]; the total dose below which there is no risk to fertility has not been established.[5] Children receiving chlorambucil before puberty generally have a normal progression of puberty.[5] In males, testicular atrophy may persist.[5] In females, potential effects on ovarian function are not known.[5]

Hyperuricemia may result from cell lysis by cytotoxic chemotherapy and may lead to electrolyte disturbances or acute renal failure.[16] 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[17]:

- aggressive hydration: 3 L/m²/24 hr with target urine output >100 ml/h
- if possible, discontinue drugs that cause hyperuricemia (e.g., thiazide diuretics) or acidic urine (e.g., salicylates)
- monitor electrolytes, calcium, phosphate, renal function, LDH, and uric acid q6h x 24-48 hours
- replace electrolytes as required
- allopurinol 600 mg po initially, then 300 mg po q6h x6 doses, then 300 mg po daily x 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.[18] It may be used for treatment or prophylaxis of hyperuricemia; however, its place in therapy has not yet been established. Aluminium hydroxide (e.g., AMPHOGEL®) may be added orally if phosphate becomes elevated. If aluminium hydroxide has been added, discontinue sodium bicarbonate.[19]

INTERACTIONS:

There are no known drug interactions with chlorambucil.[20,21]

SUPPLY AND STORAGE:

Tablets: GlaxoSmithKline supplies chlorambucil as a film coated 2 mg tablet.[3] Selected non-medicinal ingredients: lactose and synthetic red and yellow iron oxide. Store in the refrigerator.[3]

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***

Cycle Length:

Oral:

0.1 mg/kg (range 0.03-0.2 mg/kg) ***PO once daily***[3,5,6,22,23]
adjusted to induce a therapeutic response but not cause a fall in neutrophil count below 1.2 x 10^9/L
Round dose to the nearest 2 mg.
Administer on an empty stomach.

2-3 weeks[5,22,23]***:*** ***0.4 mg/kg (range 0.3-0.8 mg/kg) PO for one dose on day 1 (total dose per cycle 0.4 mg/kg [range 0.3-0.8 mg/kg]) adjusted to induce a therapeutic response but not cause a fall in neutrophil count below 1.2 x 10^9/L Round dose to the nearest 2 mg. Administer on an empty stomach.***

4-5 weeks[22]***:*** ***1 mg/kg PO daily for five days (total dose per cycle 5 mg/kg) adjusted to induce a therapeutic response but not cause a fall in neutrophil count below 1.2 x 10^9/L Round dose to the nearest 2 mg. Administer on an empty stomach.***

4 weeks[5,6]: 0.4 mg/kg (range 0.4 mg/kg- increase by 0.2 mg/kg every 4 weeks until response and/or myelosuppression occur) PO for one dose on day 1
adjusted to induce a therapeutic response but not cause a fall in neutrophil count below 1.2 x 10^9/L
Round dose to the nearest 2 mg.
Administer on an empty stomach.

6-8 weeks[22,23]***:*** ***0.2 mg/kg PO once daily for 21 consecutive days starting on day 1 (total dose per cycle 4.2 mg/kg) adjusted to induce a therapeutic response but not cause a fall in neutrophil count below 1.2 x 10^9/L Round dose to the nearest 2 mg. Administer on an empty stomach.***

Chlorambucil 2 mg/mL suspension formulation: pulverize sixty 2 mg tablets; levigate with a small amount of glycerin; add 20 mL methylcellulose and levigate until a uniform mixture is obtained; qs to 60 mLs with a 2:1 simple syrup/cherry syrup mixture; label with “refrigerate and shake well”.[7] Suspension stable 7 days when refrigerated.[7]

Concurrent radiation: additive bone marrow suppression may occur, avoid[3] or consider dose reduction when used concurrently or consecutively[4]

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: increased risk of myelosuppression[3]; no details found

Dosage in hepatic failure: dose reduction should be considered[3]; no details found

Dosage in dialysis not dialyzable[3]

Children:

		safety and effectiveness in children not established[3]; chlorambucil has been used in pediatric patients when the benefits were believed to outweigh the potential risks[5]; should be used only by physicians experienced with treating cancer in children[9]; consult a pediatric oncologist prior to use[9]
		Cycle Length:
Oral:	continuous[4,7]:	0.03-0.2 mg/kg PO once daily as a single or divided dose
	2-4 weeks[7]:	0.4 mg/kg (range 0.4-increase by 0.1 mg/kg every 2-4 weeks until response and/or myelosuppression occur) PO for one dose on day 1

REFERENCES:

1. MARTINDALE - The Complete Drug Reference (database on the Internet). Chlorambucil. Thomson MICROMEDEX®, 2006. Available at: www.micromedex.com. Accessed 4 July 2006.
2. DRUGDEX® Evaluations (database on the Internet). Chlorambucil. Thomson MICROMEDEX®, 2006. Available at: www.micromedex.com. Accessed 4 July 2006.
3. GlaxoSmithKline Inc. LEUKERAN® Product Monograph. Mississauga, Ontario; 7 January 2002.
4. USPDI® Drug Information for the Health Care Professional (database on the Internet). Chlorambucil (Systemic). Thomson MICROMEDEX®, 2006. Available at: www.micromedex.com. Accessed 4 July 2006.
5. McEvoy GK, editor. AHFS 2006 Drug Information. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc.; 2006. p. 975-978.
6. Rose BD editor. Chlorambucil: Drug Information. www.uptodate.com ed. Waltham, Massachusetts: UpToDate 14.2; 2006.
7. Rose BD editor. Chlorambucil: Pediatric drug information. www.uptodate.com ed. Waltham, Massachusetts: UpToDate 14.2; 2006.
8. Anderson PO, Knoben JE, editor. Handbook of Clinical Drug Data Eight Edition. Hamilton, Illinois: Appleton and Lange, Inc.; 1998. p. 160.
9. Hilary Wass and MD. Personal communication. Hematologist, BC Cancer Agency, Vancouver Island Cancer Centre, BC; 22 September 2006.
10. Cahill PA, Knight AW, Billinton N, et al. The GreenScreen genotoxicity assay: A screening validation programme. Mutagenesis 2004;19(2):105-119.
11. Stevenson AC, Patel C, Stevenson AC, et al. Effects of chlorambucil on human chromosomes. Mutat Res 1973;18(3):333-51.
12. Thompson-Moya L, Martin T, Heuft HG, et al. Allergic reaction with immune hemolytic anemia resulting from chlorambucil. Am J Hematol 1989;32(3):230-1.
13. Levin M, Libster D. Allergic reaction to chlorambucil in chronic lymphocytic leukemia presenting with fever and lymphadenopathy. Leukemia & Lymphoma 2005;46(8):1195-1197.
14. 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.
15. Perry M. The Chemotherapy Source Book. Baltimore, Maryland: Williams and Wilkins; 1992.
16. DeVita VT, Hellman S, Rosenberg SA. Cancer Principles & Practice of Oncology. 6th ed. Philadelphia, Pennsylvania: Lippincott Williams & Wilkins; 2001. p. 2640.
17. 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.
18. Sanofi-Synthelabo. FASTURTEC® product information. Markham, Ontario; 2004.
19. Leukemia/Bone Marrow Transplant Program of British Columbia. Leukemia/BMT Manual. E-Edition ed. Vancouver, British Columbia: Vancouver Hospital and Health Sciences Centre / BC Cancer Agency; 2010. p. 93-94.
20. Drug Interaction Facts [database on the Internet]. Chlorambucil. Facts and Comparisons 4.0, Available at: http://online.factsandcomparisons.com/. Accessed July 4, 2006.
21. Rose BD editor. Lexi-Interact™ Online. www.uptodate.com ed. Waltham, Massachusetts: UpToDate; 2006.
22. BC Cancer Agency Lymphoma Tumour Group. (LYCHLOR) BCCA Protocol Summary for Therapy for Low Grade Lymphoma and Chronic Lymphocytic Leukemia using Chlorambucil. Vancouver, British Columbia: BC Cancer Agency; 1 September 2006.
23. BC Cancer Agency Lymphoma Tumour Group. (LYPALL) BCCA Protocol Summary for Therapy for Lymphoma Palliative Chemotherapy. Vancouver, British Columbia: BC Cancer Agency; 1 September 2006.