

PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr LEUKERAN[®]

Chlorambucil Tablets USP
2 mg

Antineoplastic Agent

Aspen Pharmacare Canada Inc
111 Queen Street East, Suite 450,
Toronto, Ontario, M5C 1S2

Date of Revision:
August 23, 2017

Submission Control No: 197997

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....	3
SUMMARY PRODUCT INFORMATION	3
INDICATIONS AND CLINICAL USE.....	3
CONTRAINDICATIONS	3
WARNINGS AND PRECAUTIONS.....	4
ADVERSE REACTIONS.....	6
DRUG INTERACTIONS	8
DOSAGE AND ADMINISTRATION	8
OVERDOSAGE	9
ACTION AND CLINICAL PHARMACOLOGY	10
STORAGE AND STABILITY	11
SPECIAL HANDLING INSTRUCTIONS	11
DOSAGE FORMS, COMPOSITION AND PACKAGING	11
PART II: SCIENTIFIC INFORMATION	12
PHARMACEUTICAL INFORMATION.....	12
DETAILED PHARMACOLOGY	13
TOXICOLOGY	13
REFERENCES	14
PATIENT MEDICATION INFORMATION	21

Pr LEUKERAN®

Chlorambucil Tablets USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet / 2 mg	anhydrous lactose, colloidal silicon dioxide, hydroxypropyl methylcellulose, macrogol, microcrystalline cellulose, stearic acid, synthetic red iron oxide, synthetic yellow iron oxide and titanium dioxide

INDICATIONS AND CLINICAL USE

LEUKERAN® (chlorambucil) is indicated as monotherapy in the treatment of chronic lymphocytic leukemia. It is also indicated as monotherapy or in combination with other agents in non-Hodgkin's lymphomas including follicular lymphoma, indolent lymphoma, MALT-lymphoma, mantle-cell lymphoma; Waldenström's macroglobulinemia and Hodgkin's disease. It is not curative but produces remissions.

Geriatrics (> 65 years of age):

No data is available.

Pediatrics (< 18 years of age):

The safety and effectiveness in children have not been established.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- LEUKERAN® (chlorambucil) should not be administered to patients who are resistant to the drug or who have developed hypersensitivity to it. There may be cross-hypersensitivity (skin rash) between chlorambucil and other alkylating agents.
- Chlorambucil should not be used within four weeks of a full course of radiation or chemotherapy.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

LEUKERAN[®] (Chlorambucil) is a potent drug product and should be used only by physicians experienced with cancer chemotherapeutic drugs.

- Myelosuppression, including irreversible bone marrow failure (see WARNINGS and PRECAUTIONS Hematologic).
- Seizures (see WARNINGS and PRECAUTIONS Neurologic)
- Skin toxicity, including Stevens-Johnson syndrome and toxic epidermal necrolysis (see WARNINGS and PRECAUTIONS Skin)

General

LEUKERAN[®] (chlorambucil), a derivative of nitrogen mustard, is a potent drug. It is for use only under the direction of physicians experienced in the administration of cancer chemotherapeutic drugs.

Patients who will potentially have autologous stem cell transplantation should not be treated with chlorambucil long term.

When lymphocytic infiltration of the bone marrow is present, or the bone marrow is hypoplastic, the daily dose should not exceed 0.1 mg/kg body weight.

Carcinogenesis and Mutagenesis

Acute secondary hematologic malignancies (especially leukemia and myelodysplastic syndrome) have been reported, particularly after long term treatment (see ADVERSE EVENTS).

A comparison of patients with ovarian cancer who received alkylating agents with those who did not, showed that the use of alkylating agents including chlorambucil, significantly increased the incidence of acute leukemia.

Acute myelogenous leukemia has been reported in a small proportion of patients receiving chlorambucil as long-term adjuvant therapy for breast cancer.

The leukemogenic risk must be balanced against the potential therapeutic benefit when considering the use of chlorambucil.

Hematologic

Blood counts should be taken once or twice weekly. Discontinue or reduce the dosage upon evidence of abnormal depression of the bone marrow (see Monitoring and Laboratory Tests)

Hepatic/Biliary/Pancreatic

Consideration should be given to dose reduction in patients with gross hepatic dysfunction.

Immune

Immunisation using a live organism vaccine has a potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended.

Neurologic

Patients with nephrotic syndrome, patients prescribed high pulse dose regimens and patients with a history of seizure disorder, should be closely monitored following administration of chlorambucil, as they may have an increased risk of seizures. As with any potentially epileptogenic drug, caution should be exercised when administering chlorambucil to patients with a history of seizure disorder, head trauma, or receiving other potentially epileptogenic drugs.

Renal

Patients with evidence of impaired renal function should be carefully monitored as they are prone to additional myelosuppression associated with azotemia.

Respiratory

Severe interstitial pulmonary fibrosis has been reported in patients with chronic lymphocytic leukemia on long-term chlorambucil therapy. Pulmonary fibrosis may be reversible on withdrawal of chlorambucil.

Sexual Function/Reproduction

Chlorambucil may cause suppression of ovarian function. Amenorrhea has been reported following chlorambucil therapy.

Azoospermia has been observed as a result of therapy with chlorambucil although it is estimated that a total dose of at least 400 mg is necessary.

Varying degrees of recovery of spermatogenesis have been reported in patients with lymphoma following treatment with chlorambucil in total doses of 410 to 2600 mg.

As with other cytotoxic agents LEUKERAN[®] is potentially teratogenic.

As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised when either partner is receiving chlorambucil.

Chlorambucil has been shown to cause chromatid or chromosome damage in man.

Skin

Rare instances of skin rash progressing to erythema multiforme, toxic epidermal necrolysis, or Stevens-Johnson syndrome have been reported. Chlorambucil should be discontinued promptly in patients who develop skin reactions.

Special Populations

Pregnant Women:

The use of chlorambucil should be avoided whenever possible during pregnancy. However, when cytotoxic drugs are used in pregnancy, the possible teratogenic effect on the fetus should be kept in mind. It is therefore advisable to delay treatment with these drugs as long as possible and certainly until after the first three months of pregnancy. In any individual case, the potential hazard to the fetus must be balanced against the expected benefit to the mother.

Nursing Women: Mothers receiving LEUKERAN[®] should not breast feed.

Pediatrics (< 18 years of age): The safety and effectiveness in children have not been established.

Geriatrics (> 65 years of age): No data is available.

Monitoring and Laboratory Tests

Since LEUKERAN[®] (chlorambucil) is capable of producing irreversible bone marrow depression, blood counts should be monitored once or twice weekly in patients under treatment.

At therapeutic dosage, LEUKERAN[®] depresses lymphocytes and has less effect on neutrophil and platelet counts and on hemoglobin levels. Discontinuation of LEUKERAN[®] is not necessary at the first sign of a fall in neutrophils but it must be remembered that the fall may continue for 10 days or more after the last dose.

ADVERSE REACTIONS**Adverse Drug Reaction Overview**

For this product there is no modern clinical documentation which can be used as support for determining the frequency of undesirable effects. Undesirable effects may vary in their incidence depending on the dose received and also when given in combination with other therapeutic agents.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The following convention has been utilised for the classification of frequency:

Very common: $\geq 1/10$ ($\geq 10\%$);

Common (frequent): $\geq 1/100$ and $< 1/10$ ($\geq 1\%$ and $< 10\%$);

Uncommon (infrequent): $\geq 1/1000$ and $< 1/100$ ($\geq 0.1\%$ and $< 1\%$);

Rare: $\geq 1/10,000$ and $< 1/1000$ (≥ 0.01 and < 0.1);

Very rare: $< 1/10,000$ ($< 0.01\%$);

Not known (cannot be estimated from the available data).

Body System		Side effects
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Common	Acute secondary hematologic malignancies (especially leukemia and myelodysplastic syndrome), particularly after long term treatment.
Blood and lymphatic system disorders	Very common	Leukopenia, neutropenia, thrombocytopenia, pancytopenia or bone marrow suppression ¹ .
	Common	Anaemia.
	Very rare	Irreversible bone marrow failure.
Immune system disorders	Rare	Hypersensitivity such as urticaria and angioneurotic oedema following initial or subsequent dosing. (See Skin and subcutaneous tissue disorders)
Nervous system disorders	Common	Seizures in the paediatric population with nephrotic syndrome.
	Rare	Convulsions ² , partial and/or generalised in the paediatric population and adults receiving therapeutic daily doses or high pulse dosing regimens of chlorambucil.
	Very rare	Movement disorders including tremor, muscle twitching and myoclonus in the absence of convulsions. Peripheral neuropathy.
Respiratory, thoracic and mediastinal disorders	Very rare	Interstitial pulmonary fibrosis ³ , interstitial pneumonia.
Gastrointestinal disorders	Common	Gastro-intestinal disorders such as nausea and vomiting, diarrhoea and mouth ulceration.
Hepatobiliary disorders	Rare	Hepatotoxicity, jaundice.
Skin and subcutaneous tissue disorders	Uncommon	Rash.
	Rare	Stevens-Johnson syndrome, toxic epidermal necrolysis ⁴ . (See Immune system disorders)
Renal and urinary disorders	Very rare	Sterile cystitis.
Reproductive system and breast disorders	Not known	Amenorrhoea, azoospermia, infertility.
General disorders and administration site conditions	Rare	Pyrexia.

1. Although bone marrow suppression frequently occurs, it is usually reversible if the chlorambucil is withdrawn early enough. However, irreversible bone marrow failure has been reported. (**See Serious WARNINGS AND PRECAUTIONS**)
2. Patients with a history of seizure disorder may be particularly susceptible (see WARNINGS AND PRECAUTIONS Neurologic).
3. Severe interstitial pulmonary fibrosis has occasionally been reported in patients with chronic lymphocytic leukemia on long-term chlorambucil therapy. Pulmonary fibrosis may be reversible on withdrawal of chlorambucil. (see WARNINGS AND PRECAUTIONS Respiratory)
4. Skin rash has been reported to progress to serious conditions including Stevens-Johnson syndrome and toxic epidermal necrolysis. (see WARNINGS AND PRECAUTIONS Skin)

DRUG INTERACTIONS

Serious Drug Interactions

Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (see WARNINGS).

Animal studies indicate that patients who receive phenylbutazone may require a reduction of the standard chlorambucil doses because of the possibility of enhanced chlorambucil toxicity.

Overview

Purine nucleoside analogues (such as fludarabine, pentostatin and cladribine) increased the cytotoxicity of chlorambucil *ex vivo*; however, the clinical significance of this finding is unknown.

DOSAGE AND ADMINISTRATION

Recommended Dosage and Dosage Adjustment

Chlorambucil tablets are administered orally and should be taken daily on an empty stomach (at least one hour before meals or three hours after meals).

Chronic Lymphocytic Leukemia

Treatment with LEUKERAN[®] (chlorambucil) is usually started after the patient has developed symptoms or when there is evidence of impaired bone marrow function (but not marrow failure) as indicated by the peripheral blood count.

Initially, LEUKERAN[®] is given at the dose of 0.15 mg/kg/day until the total leukocyte count is formed to 10 000 per μL . Treatment may be resumed four weeks after the end of the first course and continued at a dosage of 0.1 mg/kg/day.

In a proportion of patients, usually after about two years of treatment, the blood leukocyte count is reduced to the normal range, enlarged spleen and lymph nodes become impalpable and the proportion of lymphocytes in the bone marrow is reduced to less than 20%.

Patients with evidence of bone marrow failure should first be treated with prednisolone and evidence of marrow regeneration should be obtained before commencing treatment with LEUKERAN[®].

Intermittent high dose therapy has been compared with daily chlorambucil but no significant difference in therapeutic response or frequency of side effects was observed between the two treatment groups.

Non-Hodgkin's Lymphoma

Used as a single agent, the usual dosage is 0.1 to 0.2 mg/kg/day for 4-8 weeks initially. Maintenance therapy is then given either by a reduced daily dosage or intermittent courses of treatment.

LEUKERAN[®] is useful in the management of patients with advanced lymphocytic lymphoma and those who have relapsed after radiotherapy.

There is no significant difference in the overall response rate obtained with chlorambucil as a single agent and combination chemotherapy in patients with advanced non-Hodgkin's lymphocytic lymphoma.

Hodgkin's Disease

Used as a single agent in the palliative treatment of advanced disease, a typical dosage is 0.2 mg/kg/day for 4-8 weeks. LEUKERAN[®] is usually included in combination therapy and a number of regimes have been used. LEUKERAN[®] may also be used as an alternative to nitrogen mustard with a reduction in toxicity but similar therapy results.

Waldenström's Macroglobulinaemia

LEUKERAN[®] is the one of the treatment choices in this indication. The following dosing regimen is recommended:

Induction: 0.1-0.2 mg/kg/day PO

Maintenance: 0.03-0.1 mg/kg/day PO

SPECIAL POPULATIONS

Renal impairment

Dose adjustment is not considered necessary in renally impaired patients.

Hepatic impairment

Patients with hepatic impairment should be closely monitored for signs and symptoms of toxicity. Since chlorambucil is primarily metabolized in the liver, dose reduction should be considered in patients with severe hepatic impairment. However, there are insufficient data in patients with hepatic impairment to provide a specific dosing recommendation.

Older people

No specific studies have been carried out in older people. However, monitoring of renal or hepatic function is advised. In the event of impairment, caution should be exercised. While clinical experience has not revealed age-related differences in response, drug dosage should be titrated carefully in older patients, usually initiating therapy at the low end of the dosage range.

OVERDOSAGE

Reversible pancytopenia was the main finding of inadvertent overdose of chlorambucil. Neurological toxicity ranging from agitated behaviour and ataxia to multiple grand mal seizures has also occurred. As there is no known antidote, the blood picture should be closely monitored

and general supportive measures should be instituted together with appropriate blood transfusion if necessary. Chlorambucil is not dialyzable. The physician should consider contacting a poison centre for additional information on the treatment of any overdose.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

LEUKERAN[®] (chlorambucil) is an aromatic nitrogen mustard derivative which acts as a bifunctional alkylating agent. Alkylation takes place through the formation of a highly reactive ethylenimonium radical. A probable mode of action involves cross-linkage of the ethylenimonium derivative between two strands of helical DNA and subsequent interference with replication. In addition to interference with DNA replication, chlorambucil induces cellular apoptosis via the accumulation of cytosolic p53 and subsequent activation of an apoptosis promoter (Bax).

Pharmacodynamics

The cytotoxic effect of chlorambucil is due to both chlorambucil and its major metabolite, phenylacetic acid mustard (see Pharmacokinetics; Metabolism)

Mechanism of resistance

Chlorambucil is an aromatic nitrogen mustard derivative and resistance to nitrogen mustards has been reported to be secondary to: alterations in the transport of these agents and their metabolites via various multi-resistant proteins, alterations in the kinetics of the DNA cross-links formed by these agents and changes in apoptosis and altered DNA repair activity. Chlorambucil is not a substrate of multi-resistant protein 1 (MRP1 or ABCC1), but its glutathione conjugates are substrates of MRP1 (ABCC1) and MRP2 (ABCC2).

Pharmacokinetics

Absorption: Chlorambucil is well absorbed by passive diffusion from the gastrointestinal tract and is measurable within 15-30 minutes of administration. The bioavailability of oral chlorambucil is approximately 70 % to 100 % following administration of single doses of 10-200 mg. In a study of 12 patients administered approximately 0.2 mg/kg of oral chlorambucil, the mean dose adjusted maximum plasma concentration (492 ± 160 nanograms/ml) occurred between 0.25 and 2 hours after administration.

Consistent with the rapid, predictable absorption of chlorambucil, the inter-individual variability in the plasma pharmacokinetics of chlorambucil has been shown to be relatively small following oral dosages of between 15 and 70 mg (2-fold intra-patient variability, and a 2-4 fold interpatient variability in AUC).

The absorption of chlorambucil is reduced when taken after food. In a study of ten patients, food intake increased the median time to reach *C_{max}* by greater than 100%, reduced the peak plasma concentration by greater than 50% and reduced mean AUC (0-∞) by approximately 27% (see Dosage & Administration).

Distribution: Chlorambucil has a volume of distribution of approximately 0.14-0.24 L/kg.

Chlorambucil covalently binds to plasma proteins, primarily to albumin (98%), and covalently binds to red blood cells.

Metabolism: Chlorambucil is extensively metabolised in the liver by monodichloroethylation and β -oxidation, forming phenylacetic acid mustard (PAAM) as the major metabolite, which possesses alkylating activity in animals. Chlorambucil and PAAM degrade in vivo forming monohydroxy and dihydroxy derivatives. In addition, chlorambucil reacts with glutathione to form mono- and diglutathionyl conjugates of chlorambucil.

Following the administration of approximately 0.2 mg/kg of oral chlorambucil, PAAM was detected in the plasma of some patients as early as 15 minutes and mean dose adjusted plasma concentration (*C_{max}*) of 306 ± 73 nanograms/ml occurred within 1 to 3 hours.

Excretion: The terminal phase elimination half-life ranges from 1.3 - 1.5 hours for chlorambucil and is approximately 1.8 hours for PAAM. The extent of renal excretion of unchanged chlorambucil or PAAM is very low; less than 1 % of the administered dose of each of these is excreted in the urine in 24 hours, with the rest of the dose eliminated mainly as monohydroxy and dihydroxy derivatives.

STORAGE AND STABILITY

LEUKERAN[®] (chlorambucil) 2 mg Tablets should be stored in a refrigerator, 2°C to 8°C.

SPECIAL HANDLING INSTRUCTIONS

Tablets should be returned to the manufacturer for destruction. Proper precautions should be taken in packaging those materials for transport.

All materials which have come in contact with cytotoxic drugs should be segregated and incinerated at 1000°C or more. Sealed containers may explode.

Personnel regularly involved in the preparation and handling of cytotoxic agents should have bi-annual blood examinations.

Provided the outer coating is intact, there is no risk to handling. LEUKERAN[®] Tablets should not be divided.

DOSAGE FORMS, COMPOSITION AND PACKAGING

LEUKERAN[®] (chlorambucil) Tablets 2 mg are brown film-coated, round, biconvex tablets engraved "GX EG3" on one face and "L" on the other face. Available in bottles of 25 tablets.

Each LEUKERAN[®] (chlorambucil) Tablet contains 2 mg chlorambucil and the non-medicinal ingredients anhydrous lactose, colloidal silicon dioxide, microcrystalline cellulose and stearic acid. The tablet coating contains: hydroxypropyl methylcellulose, macrogol, synthetic red iron oxide, synthetic yellow iron oxide and titanium dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

[As per approved PM, Control No. 180921, Page 11]

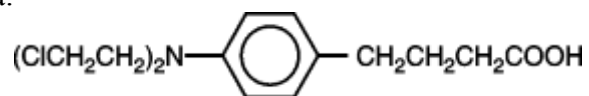
Drug Substance

Proper name: Chlorambucil

Chemical name: Benzenebutanoic acid, 4-[bis(2-chloroethyl)amino]

Molecular formula and molecular mass: $C_{14}H_{19}Cl_2NO_2$ and 304.22 g/mol

Structural formula:



Physicochemical properties:

pKa: 5.8

Description: Flattened needles from petroleum ether. Melting point of 64-66°C. Soluble at 20°C in 1.5 parts alcohol, in 2.5 parts chloroform, in 2 parts acetone. Practically insoluble in water.

DETAILED PHARMACOLOGY

LEUKERAN[®] (chlorambucil) is a derivative of nitrogen mustard first synthesized by Everett, Roberts and Ross (1953).

Haddow discovered that the substance was a powerful inhibitor of the transplanted Walker rat tumor 256, and has the pharmacological effects of nitrogen mustard compounds. Subsequent clinical investigation showed that the drug was of value in producing remissions in chronic lymphocytic leukemia and in treatment of malignant lymphomas and Hodgkin's disease. It acts as a bifunctional alkylating agent. Alkylation takes place through the formation of a highly reactive ethylenimonium radical. A probable mode of action involves crosslinkage of the ethylenimonium derivative between two strands of helical DNA and subsequent interference with replication.

The metabolism of chlorambucil in man appears to be similar to that in laboratory animals and involves β -oxidation of the butyric acid side chain. Bis-2-chloroethyl-2(4-aminophenyl) acetic acid (or phenylacetic mustard) is a major metabolite of chlorambucil; its peak plasma concentration occurs within 2-4 hours of administration of the parent drug, it has a longer terminal phase half-life than chlorambucil and it contributes significantly to the alkylating activity of the drug.

After oral administration of carbon-14 labelled chlorambucil, maximum plasma radioactivity occurs between 40 and 70 minutes later. Studies have shown that chlorambucil disappears from the plasma with a mean terminal phase half-life of 1.5 hours and that its urinary excretion is low. A high level of urinary radioactivity after oral or intravenous administration of carbon-14 labelled chlorambucil indicates that the drug is well absorbed after oral dosage.

TOXICOLOGY

Pharmacologic studies in rats showed that oral absorption is good, being slightly less than intraperitoneal absorption. A single dose of 12.5 mg/kg intraperitoneally produces typical nitrogen mustard effects. These include loss of weight the first three days, atrophy of intestinal mucosa and of lymphoid organs, severe lymphopenia becoming maximal in four days, transient mild anemia lasting ten days, and thrombocytopenia. Rapid recovery occurs, commonly within 72 hours, and the animal appears normal in about one week, although the bone marrow and blood may not become completely normal for about three weeks. An intraperitoneal dose of 18.5 mg/kg kills about 50% of the rats, with the development of convulsions. As much as 50 mg/kg has been given orally to rats as a single dose with recovery. Chlorambucil is only partially radiomimetic, producing chiefly the lymphoid effects of x-radiation as contrasted with MYLERAN (busulfan) which produces mainly the myeloid effects.

In human subjects, single oral doses of 20 mg or more may produce nausea and vomiting. In therapeutic doses, the depressant effect on the bone marrow is only moderate and rapidly reversible. Patients with lymphomas are more sensitive to the drug and smaller doses are indicated and are therapeutically useful. With excessive doses or prolonged therapy amounting to a total accumulated dosage approaching 6.5 mg/kg (about 450 mg per patient) patients may develop pancytopenia with possible irreversible bone marrow damage. Patients will usually respond to considerably less total dosage of drug than this if they are to respond at all.

REFERENCES

1. Adair CG, Bridges JM, Desai ZR. Can food affect the bioavailability of chlorambucil in patients with haematological malignancies? *Cancer Chemother Pharmacol.* 1986a;17(1):99-102 .
2. Adair CG, McElnay JC. Studies on the mechanism of gastrointestinal absorption of melphalan and chlorambucil. *Cancer Chemother Pharmacol.* 1986b;17(1):95-8.
3. AHFS Monograph: Chlorambucil. 2014, American Society of Health System Pharmacists and the Royal Pharmaceutical Society.
4. Alberts DS, Chang SY, Chen HS, Larcom BJ, Evans TL. Comparative pharmacokinetics of chlorambucil and melphalan in man. *Recent Results Cancer Res.* 1980;74:124-31.
5. Barnouin K, Leier I, Jedlitschky G, Pourtier-Manzanedo A, König J, Lehmann WD, Keppler D. Multidrug resistance protein-mediated transport of chlorambucil and melphalan conjugated to glutathione. *Br J Cancer.* 1998;77(2):201-9.
6. Barone C, Cassano A, Astone A. Toxic epidermal necrolysis during chlorambucil therapy in chronic lymphocytic leukaemia. *Eur J Cancer* 1990; 26(11/12):1262.
7. Begleiter A, Wang H, Verburg L, Lee K, Israels LG, Mowat MR, Johnston JB. In vitro cytotoxicity of 2-chlorodeoxyadenosine and chlorambucil in chronic lymphocytic leukemia. *Leukemia.* 1996a;10(12):1959-65.
8. Boesler B, Czock D, Keller F, Griesshammer M, Seufferlein T, Karges W, Rasche FM. Clinical course of haemodialysis patients with malignancies and dose-adjusted chemotherapy. *Nephrol Dial Transplant.* 2005;20(6):1187-91.
9. Bracht K, Kiefer T, Dölken G, Bednarski PJ. Characterization of three B-cell lymphoma cell lines from chemotherapy resistant patients with respect to in vitro sensitivity to 21 antitumor agents, ABC-transporter expression and cellular redox status. *J Cancer Res Clin Oncol.* 2007;133(12):957-67.
10. Calamera JC, Morgenfeld MC, Mancini RE, Vilar O. Biochemical changes of the human semen produced by chlorambucil, testosterone propionate and human chorionic gonadotropin administration. *Andrologia* 1979; 11(1):43-50.
11. Catovsky D, Galton DAG. Myelomonocytic leukemia supervening on chronic lymphocytic leukemia. *Lancet* 1971; 1(7697):478-479.
12. Callea I, Console G, Sculli G, Filangeri M, Messina G, Morabito F. Chlorambucil synergizes with purine analogs in inducing in vitro cytotoxicity in B-cell chronic lymphocytic leukemia. *Haematologica.* 1998;83(8):756-7.

13. Cheviakoff S, Calamera JC, Morgenfeld M, Mancini RE. Recovery of spermatogenesis in patients with lymphoma after treatment with chlormabucil. *J Reprod Fertil* 1973; 33:155-157.
14. Cole SR, Myers TJ, Klatsky AU. Pulmonary disease with chlorambucil therapy. *Cancer* 1978; 41(2):455-459.
15. Daoud D, Tan J, Fox N. Sterile cystitis associated with chlorambucil. *Drug Intell Clin Pharm* 1977; 11:491.
16. De Vita VT. Summary of Symposium. *Cancer Treatm Rep* 1977; 61(6):1223-1227.
17. Druker BJ, Rosenthal DS, Canellos GP. Chlorambucil, vinblastine, procarbazine, and prednisone. An effective but less toxic regimen than MOPP for advanced-stage Hodgkin's disease. *Cancer*. 1989;63(6):1060-4.
18. Ehrsson H, Lönroth U, Wallin I, Ehrnebo M, Nilsson SO. Degradation of chlorambucil in aqueous solution--influence of human albumin binding. *J Pharm Pharmacol*. 1981;33(5):313-5 .
19. Eichhorst BF, Busch R, Stilgenbauer S, Stauch M, Bergmann MA, Ritgen M, Kranzhöfer N, Rohrberg R, Söling U, Burkhard O, Westermann A, Goede V, Schweighofer CD, Fischer K, Fink AM, Wendtner CM, Brittinger G, Döhner H, Emmerich B, Hallek M. First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. *Blood*. 2009;114(16):3382-91.
20. Elias L, Stock-Novack D, Head DR, Grever MR, Weick JK, Chapman RA, Godwin JE, Metz EN, Appelbaum FR. A phase I trial of combination fludarabine monophosphate and chlorambucil in chronic lymphocytic leukemia: a Southwest Oncology Group study. *Leukemia*. 1993;7(3):361-5.
21. Enck RE, Bennett JM. Inadvertent chlorambucil overdose in adult. *NY State J Med* 1977; 77(9):1480-1485.
22. Galton DAG, Wiltshaw E, Szur L, Dacie JV. The use of chlorambucil and steroids in the treatment of chronic lymphocytic leukaemia. *Br J Haematol*. 1961;7:73-98.
23. Galton, D.A.G. *Blood and its disorders*, Chapter 21, 1974, 952-992: The chronic leukaemias. Editors: Hardisty, R.M. and Weatherall, D.J., Blackwell, Oxford.
24. Godard P, Marty JP, Michel FB. Interstitial pneumonia and chlorambucil. *Chest* 1979; 76(4):471-473.
25. Goodman GE, McLean A, Alberts DS, Chang SY. Inhibition of human tumour clonogenicity by chlorambucil and its metabolites. *Br J Cancer*. 1982;45(4):621-3.

26. Hartvig P, Simonsson B, Oberg G, Wallin I, Ehrsson H. Inter- and intraindividual differences in oral chlorambucil pharmacokinetics. *Eur J Clin Pharmacol*. 1988;35(5):551-4.
27. Hiraoka N, Kikuchi J, Yamauchi T, Koyama D, Wada T, Uesawa M, Akutsu M, Mori S, Nakamura Y, Ueda T, Kano Y, Furukawa Y. Purine analog-like properties of bendamustine underlie rapid activation of DNA damage response and synergistic effects with pyrimidine analogues in lymphoid malignancies. *PLoS One*. 2014;9(3):e90675.
28. Houot R, Le Gouill S, Ojeda Uribe M, Mounier C, Courby S, Dartigeas C, Bouabdallah K, Alexis Vigier M, Moles MP, Tournilhac O, Arakelyan N, Rodon P, El Yamani A, Sutton L, Fornecker L, Assouline D, Harousseau JL, Maisonneuve H, Caulet-Maugendre S, Gressin R. Combination of rituximab, bortezomib, doxorubicin, dexamethasone and chlorambucil (RiPAD+C) as first-line therapy for elderly mantle cell lymphoma patients: results of a phase II trial from the GOELAMS. *Ann Oncol*. 2012;23(6):1555-61.
29. Kaye SB, Juttner CA, Smith IE, Barrett A, Austin DE, Peckham MJ et al. Three years experience with ChlVPP (a combination of drugs of low toxicity) for the treatment of Hodgkin's disease. *Br J Cancer* 1979; 39(2):168-174.
30. Knisley RE, Settipane GA, Albala MM. Unusual reaction to chlorambucil in a patient with chronic lymphocytic leukemia. *Arch Dermatology* 1971; 104(1):77-79.
31. Knopse WH, Loeb V, Jr., Huguley CM, Jr. Bi-weekly chlorambucil in the treatment of chronic lymphocytic leukemia. *Cancer* 1974; 33(2):555-562.
32. Kyle R.A, Greipp P.R, Gertz M,A, Witzig T, Lust J.A, Lacy M, Therneau A.T. Waldenström's macroglobulinaemia: a prospective study comparing daily with intermittent oral chlorambucil. *British Journal of Haematology*, 2000, 108, 737-742.
33. Latta K, von Schnakenburg C, Ehrich JHH. A meta-analysis of cytotoxic treatment for frequently relapsing nephrotic syndrome in children. *Pediatric Nephrology*. 2001;16(3):271-82.
34. Lawler SD, Lele KP. Chromosomal damage induced by chlorambucil in chronic lymphocytic leukemia. *Scand J Haemat* 1972; 9(6):603-612.
35. Leblond V, Johnson S, Chevret S, Copplestone A, Rule S, Tournilhac O, Seymour J.F, Patmore R.D, Wright D, Morel P, Dilhuydy M,S, Willoughby S, Dartigeas C, Malphettes, M, Royer B, Ewings M, Pratt G, Lejeune J, Nguyen-Khac F, Choquet S, and Owen R.G. Results of a Randomized Trial of Chlorambucil Versus Fludarabine for Patients With Untreated Waldenström Macroglobulinemia, Marginal Zone Lymphoma, or Lymphoplasmacytic Lymphoma. *Journal of Clinical Oncology*. 31 (3). 2013.

36. Lerner HJ. Acute myelogenous leukemia in patients receiving chlorambucil as long term adjuvant chemotherapy for stage II breast cancer. *Cancer Treat Rep* 1978; 62(8):1135-1138.
37. Liang Y, O'Driscoll L, McDonnell S, Doolan P, Oglesby I, Duffy K, O'Connor R, Clynes M. Enhanced in vitro invasiveness and drug resistance with altered gene expression patterns in a human lung carcinoma cell line after pulse selection with anticancer drugs. *Int J Cancer*. 2004;111(4):484-93.
38. Lister TA, Cullen MH, Beard ME, Brearley RL, Whitehouse JM, Wrigley PF et al. Comparison of combined and single agent chemotherapy in non-Hodgkin's lymphoma of favourable histological type. *Br Med J* 1978; 1(6112):533-537.
39. Martindale. *The Complete Drug Reference*. 2014, The Pharmaceutical Press.
40. Mansi, J.L. ChIVPP: reducing toxicity in the treatment of Hodgkin's disease. *Eur J Cancer*, 1992, 28A/8-9, 1411-3.
41. McCallister BD, Bayrd ED, Harrison EG, McGuckin WF. Primary macroglobulinemia: review with a report on thirty-one cases and notes on the value of continuous chlorambucil therapy. *Am J Med*. 1967;43(3):394-434.
42. McElwin TJ, Toy J, Smith E, Peckham MJ, Austin DE. A combination of chlorambucil, vinblastine, procarbazine and prednisolone for the treatment of Hodgkin's disease. *Br J Cancer* 1977; 36(2):276-280.
43. McLean A, Woods RL, Catovsky D, Farmer P. Pharmacokinetics and metabolism of chlorambucil in patients with malignant disease. *Cancer Treat Rev*. 1979;6 Suppl:33-42.
44. Meyer DJ, Gilmore KS, Harris JM, Hartley JA, Ketterer B. Chlorambucil-mono-glutathionyl conjugate is sequestered by human alpha class glutathione S-transferases. *Br J Cancer*. 1992;66(3):433-8.
45. Millard LG, Rajah SM. Cutaneous reaction to chlorambucil. *Arch Dermatology* 1977; 113(9):1298.
46. Moore GE, Bross IDJ, Ausman R, Nadler S, Jones R, Slack N et al. Effects of chlorambucil (NSC-3088) in 374 patients with advanced cancer. *Cancer Chemother Rep*. 1968(PT1);52:661-66.
47. Naysmith A, Robson RH. Focal fits during chlorambucil therapy. *Postgrad Med J* 1979; 55(649):806-807.
48. Newell DR, Calvert AH, Harrap KR, McElwain TJ. Studies on the pharmacokinetics of chlorambucil and prednimustine in man. *Br J Clin Pharmacol*. 1983;15(2):253-8.
49. Nickenig C, Dreyling M, Hoster E, Ludwig WD, Dörken B, Freund M, Huber C, Ganser A, Trümper L, Forstpointner R, Unterhalt M, Hiddemann W. Initial chemotherapy with

- mitoxantrone, chlorambucil, prednisone impairs the collection of stem cells in patients with indolent lymphomas--results of a randomized comparison by the German Low-Grade Lymphoma Study Group. *Ann Oncol.* 2007;18(1):136-42.
50. Oken MM, Lee S, Kay NE, Knospe W, Cassileth PA. Pentostatin, chlorambucil and prednisone therapy for B-chronic lymphocytic leukemia: a phase I/II study by the Eastern Cooperative Oncology Group study E1488. *Leuk Lymphoma.* 2004;45(1):79-84.
 51. Pietrantonio F, Moriconi L, Torino F, Romano A, Gargovich A. Unusual reaction to chlorambucil: a case report. *Cancer Lett* 1990; 54(3):109-111.
 52. Portlock CS, Fischer DS, Cadman E, Lundberg WB, Levy A, Bobrow S et al. High-dose pulse chlorambucil in advanced low-grade non-Hodgkin's lymphoma. *Cancer Treatment Reports.* 1987;71(11):1029-31.
 53. Rai KR, Peterson BL, Appelbaum FR, Kolitz J, Elias L, Shepherd L, Hines J, Threatte GA, Larson RA, Cheson BD, Schiffer CA. Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukemia. *N Engl J Med.* 2000;343(24):1750-7.
 54. Reimer RR, Hoover R, Fraumeni JF, Jr., Young RC. Acute leukemia after alkylating-agent therapy of ovarian cancer. *New Engl J Med* 1977; 297(4):177-181.
 55. Richter P, Calamera JC, Morgenfeld MC, Kierszenbaum AL, Lavieri JC, Mancini RE. Effect of chlorambucil on spermatogenesis in the human with malignant lymphoma. *Cancer* 1970; 25(5):1026-1030.
 56. Riechelmann RP, Del Giglio A. Drug interactions in oncology: how common are they? *Ann Oncol.* 2009;20(12):1907-12.
 57. Robak J, Blonski JZ, Kasznicki M, Blasinska-Morawiec M, Krykowski E, Dmoszynska A et al. Cladribine with prednisone versus chlorambucil with prednisone as firstline therapy in chronic lymphocytic leukemia: report of a prospective, randomized, multicenter trial. *Blood.* 2000;96 (8):2723-29.
 58. Robak T, Kasznicki M. Alkylating agents and nucleoside analogues in the treatment of B cell chronic lymphocytic leukemia. *Leukemia.* 2002;16(6):1015-27.
 59. Rosenberg SA. Current concepts in cancer: non Hodgkin's lymphoma-selection of treatment on the basis of histological type. *New Engl J Med* 1979; 301(17):924-928.
 60. Rosner F. Acute leukemia as a delayed consequence of cancer chemotherapy. *Cancer* 1976; 37(2 Suppl):1033-1036.
 61. Rubio FA, Jr. Possible pulmonary effects of alkylating agents. *New Engl J Med* 1972; 287(22):1150-1151.

62. Rudd P, Fries JF, Epstein WV. Irreversible bone marrow failure with chlorambucil. *J Rheumatol* 1975; 2(4):421-429.
63. Salloum E, Khan KK, Cooper DL. Chlorambucil induced seizures. *Cancer* 1997; 79(5): 1009-1013
64. Sandler RM, Gonsalkorale M. Chronic lymphatic leukemia, chlorambucil and sensorimotor peripheral neuropathy. *Br Med J* 1977; 2(6097): 1265-1266.
65. Sawitsky A, Boklan BF, Benjamin Z. Drug fever produced by chlorambucil. *NY State J Med* 1971; 71(20):2434-2436.
66. Sieber SM, RH Adamson. Toxicity of antineoplastic agents in man; Chromosomal aberrations, antifertility effects, congenital malformations and carcinogenic potential. *Adv Cancer Res* 1975; 22:57-155.
67. Steele AJ, Prentice AG, Hoffbrand AV, Yogashangary BC, Hart SM, Nacheva EP, Howard-Reeves JD, Duke VM, Kottaridis PD, Cwynarski K, Vassilev LT, Wickremasinghe RG. p53-mediated apoptosis of CLL cells: evidence for a transcription-independent mechanism. *Blood*. 2008;112(9):3827-34.
68. Stevenson AC, Patel C. Effects of chlorambucil on human chromosomes. *Mutat Res* 1973 18(3):333-351.
69. Stout R, Todd IDH. The treatment of advanced and recurrent Hodgkin's disease with chlorambucil, vinblastine, procarbazine and prednisone in combination. *Cancer Treat Rev* 1979; 6 Suppl:107-113.
70. Summerfield GP, Taylor PRA, Mounter PJ, Proctor SJ. High-dose chlorambucil for the treatment of chronic lymphocytic leukemia and low-grade non-Hodgkin's lymphoma. *British Journal of Haematology*. 2002;116(4):781-86.
71. Taylor PR, White JM, Prescott RJ, Angus B, Galloway MJ, Jackson GH, Lessells AM, Lucraft HH, Summerfield GP, Proctor SJ, Scotland And Newcastle Lymphoma Group. The addition of oral idarubicin to a chlorambucil/dexamethasone combination has a significant impact on time to treatment failure but none on overall survival in patients with low grade non-Hodgkin's lymphoma: Results of the Scotland and Newcastle Lymphoma Group randomized NHL VIII trial. *Leuk Lymphoma*. 2006; 47(11):2321-30.
72. Treon SP, Hunter ZR, Castillo JJ, Merlini G. Waldenström macroglobulinemia. *Hematol Oncol Clin North Am*. 2014;28(5):945-70.
73. Vos JM, Minnema MC, Wijermans PW, Croockewit S, Chamuleau ME, Pals ST, Klein SK, Delforge M, van Imhoff GW, Kersten, M.J. Guideline for diagnosis and treatment of Waldenström's macroglobulinaemia. *Neth J Med*. 2013;71(2):54-62.

74. Westin J. Chromosome abnormalities after chlorambucil therapy of polycythaemia vera. *Scand J Haemat* 1976; 17(3):197-204.
75. Williams SA, Makker SP, Grupe WE. Seizures: A significant side effect of chlorambucil therapy. *Pediatric Res* 1977; 11(4):559.
76. Wiltshaw E. Chemotherapy in chronic lymphocytic leukemia. *Clin Haematol* 1977; 6(1):223-235.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Pr LEUKERAN[®]
Chlorambucil tablets, USP
(klor-AM-byoo-sil)

Read this carefully before you start taking LEUKERAN[®] and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about LEUKERAN[®].

Serious Warnings and Precautions

LEUKERAN[®] (Chlorambucil) is a potent drug and should be used only by doctors experienced with cancer, chemotherapeutic drugs.

LEUKERAN can cause severe side effects which include:

- **Myelosuppression** which is a temporary reduction in the amount of new blood cells and bone marrow cells produced by your body. This increases your risk of getting an infection.
- **Seizures** which are fits or convulsions.
- **Stevens-Johnson syndrome and toxic epidermal necrolysis** which are severe skin diseases causing rash, skin peeling and sores on mucous membranes.

What is LEUKERAN[®] used for?

LEUKERAN[®] is used to treat adult patients with cancers of the blood.

It is used:

- to treat certain forms of leukemias (cancers of the blood)
- alone or in combination with other cancer medicines to treat certain types of lymphomas (cancers of the lymph nodes which start in the white blood cells).

How does LEUKERAN[®] work?

LEUKERAN[®] belongs to a group of medicines called cytotoxics. It interferes with the growth of cancer cells which eventually are killed. Normal cells may also be affected which may lead to side effects.

What are the ingredients in LEUKERAN[®]?

Medicinal ingredient: chlorambucil

Non-medicinal ingredients: anhydrous lactose, colloidal silicon dioxide, hydroxypropyl methylcellulose, macrogol, microcrystalline cellulose, stearic acid, synthetic red iron oxide, synthetic yellow iron oxide and titanium dioxide.

LEUKERAN[®] comes in the following dosage form:

2 mg chlorambucil tablets

Do not use LEUKERAN[®] if you:

- had a severe allergic reaction to any medicine containing chlorambucil in the past
- are allergic to any of the other ingredients contained in LEUKERAN[®].
- are currently receiving, or have recently had, radiotherapy or other chemotherapy.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LEUKERAN[®]. Talk about any health conditions or problems you may have, including if you:

- had a severe allergic reaction to any ingredient in LEUKERAN[®]
- have a history of seizures (fits or convulsions). You may have an increased risk of seizures when taking LEUKERAN[®]
- are pregnant or likely to become pregnant or father a child. Reliable birth control MUST be taken to avoid pregnancy while you or your partner is taking LEUKERAN[®]
- are breastfeeding a baby
- have been vaccinated, or are planning to be vaccinated with a live vaccine
- you have or have had kidney disease
- you have or have had liver problems
- will be having surgery

Other warnings you should know about:

Myelosuppression

LEUKERAN[®] decreases the production of blood cells which can lower your blood counts. Neutropenia (a decrease in the level of white blood cells) increases your risk of getting an infection. Anemia (a decrease in the level of red blood cells) may make you tired or take longer for a minor injury to stop bleeding. Your doctor will want you to have regular blood tests while taking LEUKERAN[®]. This is to check your blood cell count and to change your dose if necessary.

Pregnancy and breast-feeding

LEUKERAN[®] may harm an unborn baby. You must tell your healthcare professional if you are or think you may be pregnant. Ask your healthcare professional for advice if you are planning to

have a baby or are breastfeeding.

Birth control in men and women

Women:

During your LEUKERAN[®] treatment, you should not become pregnant. Use an effective birth control method during this time. Talk to your healthcare professional for advice on effective methods of birth control.

Men:

You should not father a child during your LEUKERAN[®] treatment. Use condoms if you have sex while receiving LEUKERAN[®].

Cancer

LEUKERAN[®] may cause secondary cancers.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with LEUKERAN[®]:

- other medicines used to treat cancer known as purine nucleoside analogues (such as fludarabine, pentostatin and cladribine)
- phenylbutazone
- live vaccines

How to take LEUKERAN[®]:

LEUKERAN[®] will be given to you by a healthcare professional with experience in the use of cancer chemotherapeutic medicines.

Your healthcare professional will decide how much LEUKERAN[®] you will receive based on your weight and the type of cancer you have. It is important to take your medicine at the right times. You must take it in the way your doctor has told you to.

Swallow your tablets whole with a glass of water on an empty stomach (at least one hour before meals or three hours after meals). Do not break, crush or chew the tablets.

Remember: This medicine is for you. Only a doctor can prescribe it for you. Never give it to someone else. It may harm them even if their symptoms are same as yours.

Overdose:

If you think you have taken too much LEUKERAN [®] or if someone else takes your medicine by mistake, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take a dose, ask your doctor or pharmacist for advice. DO NOT double your next dose.

What are possible side effects from using LEUKERAN®?

These are not all the possible side effects you may feel when taking LEUKERAN®. If you experience any side effects not listed here, contact your healthcare professional.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Bone Marrow Suppression (a drop in the number of blood cells)		X	
Neutropenia (decreased white blood cells): aches, feeling tired, fever, flu-like symptoms, infections.		X	
Thrombocytopenia (decreased platelets in the blood); bleeding, bruising, fatigue, weakness.		X	
COMMON			
Nausea		X	
Vomiting		X	
Diarrhea (loose or watery and frequent stools)		X	
Mouth Ulcers (sores in the mouth)		X	
Acute Secondary Haematologic Malignancies (secondary blood cancers)		X	
Seizures (convulsions or fits in children with a kidney problem known as nephrotic syndrome.)		X	
Anemia (decrease in number of red blood cells): dizziness, feeling tired and weak, loss of energy, shortness of breath.		X	
UNCOMMON			
Rash		X	
RARE			
Allergic reaction: swelling of the mouth and/or throat, difficulty breathing, rash, hives, increased heart rate			X
Stevens-Johnson syndrome and toxic epidermal necrolysis (serious skin disease): rash, skin peeling and sores on mucous membranes (body openings)		X	

Jaundice (yellowing of the whites of eyes or the skin)		X	
Fever (increase in body temperature)		X	
Seizures (fits or convulsions)		X	
Hepatotoxicity (liver damage)		X	
Progressively increasing shortness of breath		X	
VERY RARE			
Abnormal and repetitive shaking of the body or twitching, without fits or convulsions		X	
Cystitis (inflammation of the bladder): pain or burning sensation while peeing. Needing to pee often and urgently.		X	
Irreversible bone marrow failure: your body may stop producing blood cells		X	
Pulmonary fibrosis (scarring and thickening of the lungs): shortness of breath		X	
Pneumonia (infection of the lungs): cough, difficult or painful breathing, fever, shortness of breath, wheezing.		X	
Peripheral neuropathy (condition affecting nerves) loss of sensation, movement and organ function		X	
NOT KNOWN			
Amenorrhoea monthly periods stop		X	
Azoospermia sperm production stops		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

<p>Reporting Side Effects</p> <p>You can report any suspected side effects associated with the use of health products to Health Canada by:</p> <ul style="list-style-type: none"> • Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or • Calling toll-free at 1-866-234-2345. <p><i>NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.</i></p>
--

Storage: Refrigerate LEUKERAN[®] at 2°C to 8°C (36°F to 46°F). Do not freeze.

Keep out of reach and sight of children.

If you want more information about LEUKERAN[®]:

- Talk to your healthcare professional
Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](http://healthcanada.gc.ca) <http://hc-sc.gc.ca/index-eng.php>; the manufacturer's website www.aspenpharma.ca, or by calling 1-844-330-1213.

This leaflet was prepared by:
Aspen Pharmacare Canada Inc
111 Queen Street East, Suite 450,
Toronto, Ontario, M5C 1S2

Last Revised: August 23, 2017

[®]LEUKERAN is a registered trademark of Aspen. All rights reserved.