PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# PrLEUKERAN®

Chlorambucil Tablets USP
2 mg

Antineoplastic Agent

Aspen Pharmacare Canada Inc
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## RECENT MAJOR LABEL CHANGES

| | |
|---|---|
| Dosage and Administration, Recommended Dose and Dosage Adjustment (4.1) | 08/2017 |
| Warnings and Precautions (7) | 08/2017 |

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## PART I: HEALTH PROFESSIONAL INFORMATION

## 1 INDICATIONS

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.

### 1.1 Pediatrics

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

### 1.2 Geriatrics

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

## 2 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, STRENGTHS, 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.

## 3 SERIOUS WARNINGS AND PRECAUTIONS BOX

**Serious Warnings and Precautions**

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

- Myelosupression, 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)

# 4 DOSAGE AND ADMINISTRATION

## 4.1 Dosing Considerations

- ***Geriatrics:*** 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 (See ACTION AND CLINICAL PHARMACOLOGY/Pharmacokinetics/Special Populations and Conditions).

- ***Hepatic Insufficiency:*** 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 (See ACTION AND CLINICAL PHARMACOLOGY/Pharmacokinetics/Special Populations and Conditions).

## 4.2 Recommended Dose 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

Health Canada has not authorized an indication for pediatric (<18 years of age) use.
(see INDICATIONS/Pediatrics)

## 5 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.

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table – Dosage Forms, Strengths, Composition and Packaging.**

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal 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 |

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.

## 7 WARNINGS AND PRECAUTIONS

Please see the Serious Warnings and Precautions Box at the beginning of Part I: Health Professional Information.

### 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 REACTIONS).

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.

### Driving and Operating Machinery

Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

### 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.

**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.

**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.

### 7.1 Special Populations

#### 7.1.1 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.

#### 7.1.2 Breast-feeding

Mothers receiving LEUKERAN® should not breast feed.
It is unknown if the drug is excreted in human milk. Because many drugs are excreted in human milk precaution should be exercised.

#### 7.1.3 Pediatrics

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

#### 7.1.4 Geriatrics

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

## 8 ADVERSE REACTIONS

### 8.1 Adverse 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.

### 8.2 Clinical Trial Adverse 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: ≥1/10 (≥10%);
Common (frequent): ≥1/100 and <1/10 (≥1% and <10%);
Uncommon (infrequent): ≥1/1000 and <1/100 (≥0.1% and <1%);
Rare: ≥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 | Hepatoxicity, 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)

# 9 DRUG INTERACTIONS

## 9.1 Serious Drug Interactions Box

**Serious Drug Interactions**

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

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.

## 9.2 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.

# 10 ACTION AND CLINICAL PHARMACOLOGY

## 10.1 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).

## 10.2 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).

### 10.3 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.

**Special Populations and Conditions**

***Geriatrics:*** 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 (See DOSAGE AND ADMINISTRATION/Dosing Considerations).

***Hepatic Insufficiency:*** Patients with hepatic impairment should be closely monitored for signs

and symptoms of toxicity (See DOSAGE AND ADMINISTRATION/Dosing Considerations).

***Renal Insufficiency:*** Dose adjustment is not considered necessary in renally impaired patients.

## 11 STORAGE, STABILITY AND DISPOSAL

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

## 12 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 1000ºC 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.

## PART II: SCIENTIFIC INFORMATION

## 13 PHARMACEUTICAL INFORMATION

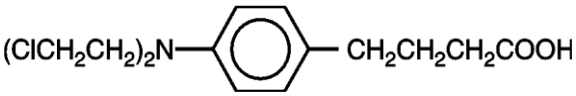
### Drug Substance

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.

## 14 NON-CLINICAL 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.

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**PATIENT MEDICATION INFORMATION**

**PrLEUKERAN®**
**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.

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- 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.

*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.*

**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://hc-sc.gc.ca/index-eng.php; the manufacturer's website www.aspenpharma.ca, or by calling 1-844-330-1213.

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