

NEW ZEALAND DATA SHEET

1. LEUKERAN® Tablets

chlorambucil tablets 2 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg of chlorambucil.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

LEUKERAN tablet 2 mg is a brown, film-coated tablet that is round, normal, biconvex, and engraved with "GX EG3" on one face and "L" on the other face.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

LEUKERAN is indicated in the treatment of:-

- Hodgkin's disease
- certain forms of non-Hodgkin's lymphoma
- chronic lymphocytic leukaemia
- Waldenstrom's macroglobulinaemia
- Advanced ovarian adenocarcinoma.

Leukeran has a significant therapeutic effect on a proportion of patients with breast cancer.

4.2 Dose and method of administration

THE RELEVANT LITERATURE SHOULD BE CONSULTED FOR FULL DETAILS OF THE TREATMENT SCHEDULES USED.

LEUKERAN is an active cytotoxic agent for use only under the direction of physicians experienced in the administration of such agents.

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

Adults

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 has been used as an alternative to nitrogen mustard with a reduction in toxicity but similar therapeutic results.

Non-Hodgkin's lymphoma:-

Used as a single agent the usual dosage is 0.1-0.2 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 diffuse 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.

Chronic lymphocytic leukaemia:-

Treatment with LEUKERAN 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 a dosage of 0.15 mg/kg/day until the total leukocyte count has fallen to 10,000 per microL. Treatment may be resumed 4 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 2 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 per cent.

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 LEUKERAN but no significant difference in therapeutic response or frequency of side effects was observed between the two treatment groups.

Waldenstrom's macroglobulinaemia:-

LEUKERAN is the treatment of choice in this indication.

Starting doses of 6-12 mg daily until leucopenia occurs are recommended followed by 2-8 mg daily indefinitely.

Ovarian carcinoma:-

Used as a single agent a typical dosage is 0.2 mg/kg/day for 4-6 weeks.

A dosage of 0.3 mg/kg/day has been given until leucopenia had been induced.

Maintenance dosage of 0.2 mg/kg/day has been given aiming to keep the total leukocyte count below 4,000/mm³.

In practice, maintenance courses tend to last 2-4 weeks with intervals of 2-6 weeks between each course.

Advanced breast cancer:

Used as a single agent a typical dosage is 0.2 mg/kg bodyweight per day for 6 weeks.

LEUKERAN may be given in combination with prednisolone at a dose range of 14-20 mg daily regardless of bodyweight, over 4-6 weeks provided there is no serious haemopoietic depression.

LEUKERAN may be given in combination with methotrexate, 5-fluorouracil, and prednisolone at a dosage of 5 to 7.5 mg/m²/day.

Children

LEUKERAN may be used in the management of Hodgkin's disease and non-Hodgkin's lymphomas in children. The dosage regimens are similar to those used in adults.

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.

4.3 Contraindications

In view of the seriousness of the indications there are no absolute contraindications.

4.4 Special warnings and special precautions for use

LEUKERAN IS AN ACTIVE CYTOTOXIC AGENT FOR USE ONLY UNDER THE DIRECTION OF PHYSICIANS EXPERIENCED IN THE ADMINISTRATION OF SUCH AGENTS.

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

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

Monitoring:-

Since LEUKERAN is capable of producing irreversible bone marrow suppression, blood counts should be closely monitored in patients under treatment.

At therapeutic dosage LEUKERAN depresses lymphocytes and has less effect on neutrophil and platelet counts and on haemoglobin 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.

LEUKERAN should not given to patients who have recently undergone radiotherapy or received other cytotoxic agents.

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 bodyweight.

Children with nephrotic syndrome, patients prescribed high pulse dosing regimens and patients with a history of seizure disorder, should be closely monitored following administration of LEUKERAN, as they may have an increased risk of seizures.

Mutagenicity and carcinogenicity:-

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

Acute secondary haematologic malignancies (especially leukaemia and myelodysplastic syndrome) have been reported, particularly after long term treatment (see section 4.8, Undesirable effects).

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 leukaemia.

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

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

4.5 Interaction with other medicines and other forms of interaction

Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (see section 4.4, Special warnings and precautions for use).

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

4.6 Fertility, pregnancy and lactation

Fertility:-

Chlorambucil may cause suppression of ovarian function and amenorrhoea 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 410-2600 mg.

Pregnancy:-

The use of chlorambucil should be avoided whenever possible during pregnancy, particularly during the first trimester. In any individual case, the potential hazard to the foetus must be balanced against the expected benefit to the mother.

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

Lactation:-

Mothers receiving LEUKERAN should not breastfeed.

Teratogenicity:-

As with other cytotoxic agents LEUKERAN is potentially teratogenic.

4.7 Effects on ability to drive and use machines

No data available.

4.8 Undesirable effects

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.

The following convention has been utilised for the classification of frequency: Very common ($\geq 1/10$), common ($\geq 1/100$ and $< 1/10$), uncommon ($\geq 1/1000$ and $< 1/100$), rare ($\geq 1/10,000$ and $< 1/1000$), very rare ($< 1/10,000$)_and not known (cannot be estimated from the available data).

<u>Body System</u>		<u>Side Effects</u>
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Common	Acute secondary haematologic malignancies (especially leukaemia 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. (<i>see Skin and subcutaneous tissue disorders</i>)
Nervous system disorders	Common	Convulsions in children with nephrotic syndrome
	Rare	Convulsions ² , partial and/or generalised in children and adults receiving therapeutic daily doses or high pulse dosing regimens of chlorambucil. Movement disorders including tremor, muscle twitching and myoclonus in the absence of convulsions. Tremors and muscular twitching resolve upon

		discontinuation of drug.
	Very rare	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. Other side effects may be encountered but usually only when the therapeutic dosage has been exceeded.
Hepatobiliary disorders	Rare	Hepatotoxicity, jaundice.
Skin and subcutaneous tissue disorders	Uncommon	Rash.
	Rare	erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis. ⁴ (see <i>Immune system disorders</i>)
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 chlorambucil is withdrawn early enough.

2. Patients with a history of seizure disorder may be particularly susceptible.

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

4. Skin rash has been reported to progress to serious conditions including Stevens- Johnson syndrome and toxic epidermal necrolysis.

The most common side effect is bone marrow suppression. 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.

Acute secondary haematologic malignancies (especially leukaemia and myelodysplastic syndrome), particularly after long term treatment have occurred in patients treated with chlorambucil.

Leukopenia, neutropenia, thrombocytopenia and pancytopenia occurs very commonly while anaemia is commonly reported.

Gastro-intestinal disturbances such as nausea and vomiting, diarrhoea and oral ulceration occur infrequently. Other side effects may be encountered but usually only when the therapeutic dosage has been exceeded.

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

Hepatotoxicity and jaundice have been reported.

Allergic reactions to LEUKERAN such as urticaria and angioneurotic oedema have been rarely reported following initial or subsequent dosing. Skin rashes are uncommon but have on very rare occasions been reported to progress to serious conditions including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Other reported adverse reactions include fever, peripheral neuropathy, interstitial pneumonia and sterile cystitis.

Seizures have occurred in children with nephrotic syndrome treated with chlorambucil. Rare, focal and/or generalised seizures have been reported to occur in children and adults receiving therapeutic daily doses or high pulse dosing regimens of chlorambucil. Patients with a history of seizure disorder may be particularly susceptible.

Movement disorders including tremor, twitching and myoclonia in the absence of convulsions have also been reported.

{Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>}

4.9 Overdose

Reversible pancytopenia was the main finding of inadvertent overdoses 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.

{For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).}

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Chlorambucil is an aromatic nitrogen mustard derivative which acts as a bifunctional alkylating agent. 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).

The cytotoxic effect of chlorambucil is due to both chlorambucil and its major metabolite, phenylacetic acid mustard (see section 5.2, 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).

5.2 Pharmacokinetic Properties

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 ng/mL) occurred between 0.25 and 2 hours after administration. The mean (\pm SD) terminal plasma elimination half-life was 1.3 ± 0.5 hours.

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 section 4.2, Dosage & method of 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.

Elimination

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.

5.3 Preclinical Safety Data

Mutagenicity and Carcinogenicity

As with other cytotoxic agents chlorambucil is mutagenic in in vitro and in vivo genotoxicity tests and carcinogenic in animals and humans.

Effects on fertility

In rats, chlorambucil has been shown to damage spermatogenesis and cause testicular atrophy.

Teratogenicity

Chlorambucil has been shown to induce development abnormalities, such as short or kinky tail, microcephaly and exencephaly, digital abnormalities including ectro-, brachy-, syn-, and polydactyly and long-bone abnormalities such as reduction in length, absence of one or

more components, total absence of ossification sites in the embryo of mice and rats following a single oral administration of 4-20 mg/kg. Chlorambucil has also been shown to induce renal abnormalities in the offspring of rats following a single intraperitoneal injection of 3-6 mg/kg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core: microcrystalline cellulose, anhydrous lactose, colloidal anhydrous silica, stearic acid

Tablet film coating: hypromellose, titanium dioxide, synthetic yellow, iron oxide, synthetic red iron oxide, macrogol. **Incompatibilities**
No data available.

6.2 Incompatibilities

No data available.

6.3 Shelf Life

36 months.

6.4 Special precautions for storage

Store between 2°C and 8°C (Refrigerate, do not freeze). Protect from light.

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

Package Quantities
Bottles (glass) of 25 tablets.

6.6 Special precautions for disposal <and other handling>

Safe handling of LEUKERAN tablets:-

The handling of LEUKERAN tablets should follow guidelines for the handling of cytotoxic agents according to prevailing local recommendations and/or regulations (for example, Royal Pharmaceutical Society of Great Britain Working Party on the Handling of Cytotoxic Drugs (Working Party Report, 1983, and subsequent Amendment, 1987)).

LEUKERAN Tablets should not be divided. Provided the outer coating of the tablet is intact, there is no risk in handling LEUKERAN Tablets (Working Party Report, 1983).

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Pharmacy Retailing Pty Ltd
t/a Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Auckland
New Zealand

9. DATE OF FIRST APPROVAL

08 November 2006

10. DATE OF REVISION OF THE TEXT

April 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All sections revised	Update to the SPC-style format