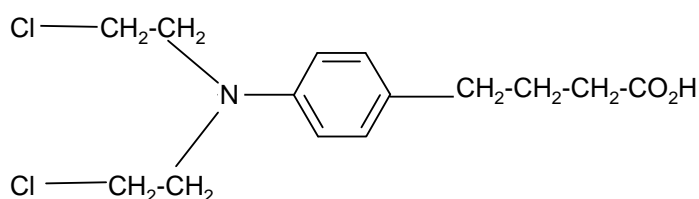


PRODUCT INFORMATION

LEUKERAN[®] TABLETS

NAME OF THE DRUG:

The chemical name for chlorambucil is 4-[bis(2-chloroethyl)amino] benzenebutanoic acid, it has a molecular weight of 304.2, its molecular formula is C₁₄H₁₉Cl₂NO₂, CAS No.: 305-03-3 and the chemical structure is:



Leukeran tablets contain 2 mg chlorambucil.

DESCRIPTION:

Chlorambucil is a white or off-white crystalline or granular powder. It is practically insoluble in water, freely soluble in acetone and in alcohol.

Each Leukeran tablet contains the following excipients: anhydrous lactose, cellulose - microcrystalline, silica - colloidal anhydrous, stearic acid, hypromellose, titanium dioxide, macrogol 400, iron oxide yellow (CI77492) and iron oxide red (CI77491).

PHARMACOLOGY:

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 2 strands of helical DNA and subsequent interference with replication.

PHARMACOKINETICS:

After oral administration of ¹⁴C-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 life of 1.5 hours and that its urinary excretion is low. A high level of urinary radioactivity after oral or intravenous administration of ¹⁴C-labelled chlorambucil indicates that the drug is rapidly and completely absorbed from the gastrointestinal tract after oral dosage.

In a study of 12 patients administered chlorambucil 0.2mg/kg body weight orally, the mean dose adjusted-maximum plasma concentration of chlorambucil (492 ± 160 ng/mL) occurred between 0.25 and 2 hours after administration. The mean (± SD) terminal plasma elimination half-life was 1.3 ± 0.5 hours.

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-chlorethyl-2(4-aminophenyl) acetic acid [phenylacetic acid mustard (PAAM)] is a major metabolite of chlorambucil. Chlorambucil and its metabolites are extensively bound to plasma and tissue proteins. In vitro, chlorambucil is 99% bound to plasma proteins, specifically albumin. In a study of 12 patients administered chlorambucil 0.2mg/kg body weight orally, the mean dose adjusted-peak plasma concentration of PAAM (306 ± 73 ng/mL) was reached within 1-3 hours. The mean terminal elimination plasma half-life was 1.8 ± 0.4 hours. The significant contribution of PAAM to the alkylating activity of the drug was evident as the mean area under the plasma concentration time curve (AUC) of PAAM was approximately 1.33 times greater than the AUC of chlorambucil.

INDICATIONS:

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 effect in a proportion of patients with breast cancer.

CONTRAINDICATIONS:

Chlorambucil should not be used in patients whose disease has demonstrated a prior resistance to the agent. Leukeran is contraindicated in patients with known hypersensitivity to chlorambucil or to any ingredient of the preparation.

PRECAUTIONS:

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.

Safe handling of LEUKERAN Tablets:

The handling of LEUKERAN Tablets should follow standard guidelines for the handling of cytotoxic drugs.

Provided the outer coating of the tablet is intact, there is no risk in handling LEUKERAN Tablets. LEUKERAN Tablets should not be divided.

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 be 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. As with any potentially epileptogenic drug, caution should be exercised when administering chlorambucil to patients with a history of seizure disorder, or head trauma, or who are receiving other potentially epileptogenic drugs.

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

Hepatic Impairment: The metabolism of LEUKERAN is still under investigation and consideration should be given to dose reduction in patients with gross hepatic dysfunction.

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.

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 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 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.

Teratogenicity: Chlorambucil has been shown to induce developmental 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.

Effects on 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 to 2600 mg.

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

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

Use in Pregnancy: (Category D)

As with other cytotoxic agents, LEUKERAN can produce spontaneous abortion, foetal loss and birth defects. 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.

Use in Lactation:

Mothers receiving LEUKERAN should not breastfeed.

ADVERSE REACTIONS:

Hematologic: The most common side effect is bone marrow suppression including, very commonly: leucopenia, neutropenia, thrombocytopenia, pancytopenia and, commonly: anaemia. Although this 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 been reported.

Gastrointestinal: Gastrointestinal 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.

Dermatologic: Allergic reactions to Leukeran such as urticaria and angioneurotic oedema have been rarely reported following initial or subsequent dosing. Skin hypersensitivity (including rare reports of skin rash progressing to erythema multiforme, toxic epidermal necrolysis, and Stevens-Johnson syndrome) has been reported.

CNS: Movement disorders including tremor, twitching and myoclonia in the absence of convulsions have also been reported. Tremors and muscular twitching have been reported as rare adverse experiences to chlorambucil which resolve upon discontinuation of drug. 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.

Other: Severe interstitial pulmonary fibrosis has occasionally been reported in patients with chronic lymphocytic leukaemia on long-term chlorambucil therapy. However, this may be reversible on withdrawal of chlorambucil. Hepatotoxicity and jaundice have been reported after chlorambucil treatment. Other reported adverse reactions include fever, peripheral neuropathy, interstitial pneumonia, sterile cystitis, infertility, and leukaemia.

INTERACTIONS:

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

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.

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.

OVERDOSAGE:

Treatment: 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. Chlorambucil is not dialysable.

DOSAGE AND ADMINISTRATION:

The literature should be consulted for full details of the treatment schedules used.

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

Hodgkin's disease: Used as a single agent a typical dosage is 0.2 mg/kg/day for four to eight weeks. LEUKERAN is usually included in combination therapy and a number of regimens have been used. LEUKERAN may also be 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 to 0.2 mg/kg/day for four to eight 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 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 leucocyte count has fallen to 10 000/microlitre. Treatment may be resumed 4 weeks after the end of the first course and continued at dosage of 0.1 mg/kg/day.

In a proportion of patients, usually after about 2 years of treatment, the blood leucocyte 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.

Waldenstrom's Macroglobulinaemia: LEUKERAN is the treatment of choice in this indication. Starting doses of 6 to 12 mg daily until leucopenia occurs are recommended followed by 2 to 8 mg daily indefinitely.

Ovarian Carcinoma: Used as a single agent a typical dosage is 0.2 mg/kg/day for four to six 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 leucocyte count below 4000/mm³. In practice maintenance courses tend to last 2 to 4 weeks with intervals of 2 to 6 weeks between each course.

Advanced Breast Cancer: Used as a single agent a typical dosage is 0.2 mg/kg/day for six weeks. LEUKERAN may be given in combination with prednisolone at a dose range of 14 to 20 mg daily, regardless of bodyweight, over four to six weeks provided there is no serious haemopoietic depression. LEUKERAN may also 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

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.

PRESENTATION:

Leukeran tablets are brown film-coated, round, biconvex tablets engraved "GX EG3" on one side and "L" on the other. They each contain 2 mg chlorambucil and are supplied in bottles of 25 and 50* tablets.

(*not currently distributed in Australia)

Storage: Store at 2°C to 8°C. (Refrigerate. Do not freeze). Protect from light.

Poison schedule: S4.

SPONSOR:

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Approved by the Therapeutic Goods Administration on 23 November 2000.

Date of most recent amendment: 27 April 2011

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