LEUKERAN™

Chlorambucil

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg of the active ingredient chlorambucil.

PHARMACEUTICAL FORM

Film-coated tablet.

CLINICAL PARTICULARS

Indications

LEUKERAN is indicated in the treatment of:

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

Dosage and 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 to 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 to 0.2 mg/kg/day for 4 to 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 *LEUKERAN* 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 microlitre. 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 one of the treatment choices in this indication.
Starting doses of 6 to 12 mg daily until leukopenia occurs are recommended followed by 2 to 8 mg daily indefinitely.

- **Paediatric population**

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

- 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 the older patients. 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.

Contraindications

Hypersensitivity to chlorambucil or to any of the excipients.

Warnings and Precautions

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 *LEUKERAN* long term.

Safe handling of *LEUKERAN* Tablets: See Instructions for Use/Handling.

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.

Mutagenicity and carcinogenicity

LEUKERAN 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 *LEUKERAN*, significantly increased the incidence of acute leukaemia.

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

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

Interactions

Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (*see Warnings and Precautions*).

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.

Pregnancy and Lactation

Fertility

Chlorambucil may cause suppression of ovarian function and amenorrhoea has been reported following *LEUKERAN* therapy.

Azoospermia has been observed as a result of therapy with *LEUKERAN* 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 *LEUKERAN* in total doses of 410 to 2600 mg.

Pregnancy

The use of *LEUKERAN* 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 other cytotoxic agents, adequate contraceptive precautions should be advised when either partner is receiving *LEUKERAN*.

Breastfeeding

Mothers receiving *LEUKERAN* should not breastfeed.

Teratogenicity

As with other cytotoxic agents chlorambucil is potentially teratogenic. *(see Pre-clinical Safety Data)*

Effects on Ability to Drive and Use Machines

No data.

Adverse Reactions

For this product there is no modern clinical documentation which can be used 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 used for the classification of frequency: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000), very rare (<1/10,000), and 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 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. *(See Skin and subcutaneous tissue disorders)*
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 *LEUKERAN*.
	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.
General disorders and administration site conditions	Rare	Pyrexia.

1. Although bone marrow suppression frequently occurs, it is usually reversible if *LEUKERAN* 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 *LEUKERAN* therapy. However, this may be reversible on withdrawal of *LEUKERAN*.
4. Skin rash has been reported to progress to serious conditions including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Overdose

Symptoms and signs

Reversible pancytopenia was the main finding of inadvertent overdoses of *LEUKERAN*. Neurological toxicity ranging from agitated behaviour and ataxia to multiple grand mal seizures has also occurred.

Treatment

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC Code

L01AA02

Mechanism of Action

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).

Pharmacodynamic Effects

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 ng/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 (Cmax) 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.

Pre-clinical 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.

Reproductive toxicology

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

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 to 20 mg/kg. Chlorambucil has also been shown to induce renal abnormalities in the offspring of rats following a single intraperitoneal injection of 3 to 6 mg/kg.

Brain and plasma pharmacokinetics

After oral administration of 14C-marked chlorambucil to rats, the highest concentrations of radioactive marked material were found in the plasma, in the liver and in the kidneys. Only small concentrations were measured in the cerebral tissue of rats after intravenous administration of chlorambucil.

PHARMACEUTICAL PARTICULARS

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

None known.

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

Store at 2°C to 8°C.

Nature and Contents of Container

LEUKERAN tablets are brown film-coated, round, biconvex tablets engraved “GX EG3” on one side and “L”on the other, supplied in amber glass bottles with a child resistant closure.

Instructions for Use/Handling

Safe handling of *LEUKERAN* tablets

The handling of *LEUKERAN* tablets should follow guidelines for the handling of cytotoxic drugs according to prevailing local recommendations and/or regulations (for example, Royal Pharmaceutical Society of Great Britain Working Party on 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.

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