Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Leukeran 2 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg of the active ingredient chlorambucil.

Excipient(s) with known effect:
Each tablet also contains 67.65 mg of lactose.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet. (Tablet).
Brown, round, biconvex tablet, engraved on one side with “L” and “GX EG3” on the other.

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.

4.2 Posology and method of administration

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

LEUKERAN IS AN ACTIVE CYTOTOXIC AGENT AND SHOULD ONLY BE ADMINISTERED UNDER THE DIRECTION OF A SPECIALIST ONCOLOGY SERVICE HAVING THE FACILITIES FOR REGULAR MONITORING OF CLINICAL BIOCHEMICAL AND HAEMATOLOGICAL EFFECTS DURING AND AFTER ADMINISTRATION.

Posology

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 microliter.
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 6-12 mg daily until leukopenia occurs are recommended followed by 2-8 mg daily indefinitely.

SPECIAL POPULATIONS

Renal impairment

Chlorambucil has an extremely low urinary excretion and hence renal excretion is not considered an important pathway in chlorambucil elimination. Dose adjustment is not considered necessary in renally impaired patients. However no formal studies of the effects of renal insufficiency on the pharmacokinetics of chlorambucil have been carried out.

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.

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

Use in the elderly
No specific studies have been carried out in the elderly, however, it may be advisable to monitor renal or hepatic function and if there is impairment then caution should be exercised.
While clinical experience has not revealed age-related differences in response, drug dosage generally should be titrated carefully in elderly patients, usually initiating therapy at the low end of the dosage range.

Method of administration
Leukeran is taken orally. High gastric pH has been shown to significantly decrease the bioavailability of Leukeran therefore ingestion on an empty stomach (one hour before a meal or 3 hours after) is advised.

4.3 Contraindications

Use in the management of patients with non-malignant disease.
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised individuals. 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.

Safe handling of Leukeran Tablets
See section 6.6.

Monitoring
Since Leukeran is capable of producing irreversible bone marrow suppression, blood counts should be closely monitored in patients under treatment. Total dosage in the region of 6.5 mg/kg bodyweight is associated with the risk of irreversible bone marrow damage.

At therapeutic dosage Leukeran depresses lymphocytes and has less although progressive 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. Leukeran should only be used with caution in patients with depressed bone narrow function or lymphocytic infiltration of same. 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.

The paediatric population with nephrotic syndrome, patients prescribed as 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 and has been shown to be carcinogenic in animals. The possibility of a similar effect should be borne in mind when designing the long-term management of the patient. Acute secondary haematologic malignancies (especially leukaemia and myelodysplastic syndrome) have been reported, particularly after long term treatment (see section 4.8). 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.

Sugar intolerances
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

Vaccinations with live organism vaccines are not recommended in immunocompromised individuals (see section 4.4).
Purine nucleoside analogues (such as fludarabine, pentostatin and cladribine) increased the cytotoxicity of chlorambucil *ex vivo*. Clinically the combination of purine nucleoside analogues and alkylating agents have been shown to produce high disease response rates however the combinations have also resulted in higher rates of haematological toxicities. 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised when either partner is receiving Leukeran. Partners should be informed of the drugs affect on germ cells. This product should not be used in pregnancy, particularly in the first trimester, unless considered absolutely essential by the physician.

Breast-feeding
Mothers receiving Leukeran should not breast-feed.

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 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.

Teratogenicity

As with other cytotoxic agents Leukeran is potentially teratogenic (see section 5.3).

4.7 Effects on ability to drive and use machines

No information on the effects of Chlorambucil on the ability to drive and use machines is 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 (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10,000 and <1/1000) and very rare (<1/10,000), 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.
Nervous system disorders	Common	Convulsions 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].

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 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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via: HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2. Tel: +353 1 6764971; Fax: +353 1 6762517; Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms and signs
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.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antineoplastic and immunomodulating agents, antineoplastic agents, alkylating agents, nitrogen mustard analogues, 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 section 5.2).

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 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 oraldosages 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).

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.

Biotransformation
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 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core
Microcrystalline cellulose

Lactose, anhydrous
Colloidal anhydrous silica
Stearic acid

Coat
Hypromellose
Titanium dioxide
Macrogol/ PEG 400
Synthetic red and yellow iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator between 2°C - 8°C. Store in the original container.

6.5 Nature and contents of container

Leukeran tablets are supplied in amber (Type III) glass bottles with a child resistant polypropylene/HDPE closure containing 25 and 50 tablets.
Not all pack sizes may be marketed.

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 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 handling Leukeran Tablets. Pregnant staff should not handle cytotoxic agents. Leukeran Tablets should not be divided.

7 MARKETING AUTHORISATION HOLDER

Aspen Pharma Trading Limited
3016 Lake Drive
Citywest Business Campus
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1691/007/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1979
Date of last renewal: 01 April 2009

10 DATE OF REVISION OF THE TEXT

June 2022