1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

LEUKERAN 2 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of LEUKERAN 2 mg contains 2 mg of chlorambucil.

Contains sugar: Lactose anhydrous 67,65 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

LEUKERAN 2 mg are brown, round, biconvex, film-coated tablets, one side engraved with “L” and the other side engraved “GX EG3.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

LEUKERAN 2 mg 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

Posology

Adults

LEUKERAN 2 mg, is administered orally and should be taken daily on an empty stomach (at least one hour before meals or three hours after meals). LEUKERAN 2 mg should not be divided (see section 4.4).

Hodgkin's disease:

Adults

Used as a single medicine in the palliative treatment of advanced disease a typical dosage is 0,2 mg/kg/day for three to eight weeks.

LEUKERAN 2 mg, is usually included in combination therapy and a number of regimes have been used.

Paediatric population

LEUKERAN 2 mg, may be used in the management of Hodgkin's disease in children. The dosage regimens are similar to those used in adults.

Non-Hodgkin's lymphoma:

Adults

Used as a single medicine 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 2 mg, may be used 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 medicine and combination chemotherapy in patients with advanced non-Hodgkin's lymphocytic lymphoma.

Paediatric population

LEUKERAN 2 mg, may be used in the management of non-Hodgkin's disease in children. The dosage regimens are similar to those used in adults.

Chronic lymphocytic leukaemia:

Adults

Treatment with LEUKERAN 2 mg, 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 2 mg, is given at a dosage of 0,15 mg/kg/day until the total leukocyte count has fallen to 10 000 per µl. 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 %.

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 2 mg.

Intermittent high-dose therapy has been compared with daily LEUKERAN 2 mg but no significant difference in therapeutic response or frequency of side effects was observed between the two treatment groups.

Waldenstrom's macroglobulinaemia:

Adults

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

Method of administration

For oral administration.

4.3. Contraindications

LEUKERAN 2 mg is contraindicated in:

- Patients with hypersensitivity to chlorambucil or to any excipients in LEUKERAN 2 mg (see section 6.1).

- Concomitant vaccination with live vaccines. Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are contraindicated in patients using LEUKERAN 2 mg.
- Pregnancy and lactation (see section 4.6).

4.4. Special warnings and precautions for use

LEUKERAN 2 mg IS A CYTOTOXIC MEDICINE FOR USE ONLY UNDER THE DIRECTION OF MEDICAL PRACTITIONERS EXPERIENCED IN THE ADMINISTRATION OF SUCH MEDICINES.

Autologous stem cell transplantation

Patients who will potentially have autologous stem cell transplantation should not be treated with LEUKERAN 2 mg.

Monitoring

Since LEUKERAN 2 mg is capable of producing irreversible bone marrow suppression, blood counts should be closely monitored in patients under treatment.

At therapeutic dosage LEUKERAN 2 mg depresses lymphocytes and has less effect on neutrophil and platelet counts and on haemoglobin levels.

Discontinuation of LEUKERAN 2 mg 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 2 mg should not be given to patients who have recently undergone radiotherapy or received other cytotoxic medicines.

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 2 mg, as they may have an increased risk of seizures.

Weekly clinical and haematological examinations should be made, and it is not safe to omit them for more than two weeks as irreversible bone marrow damage may occur. Total and differential blood cell counts, and the estimation of haemoglobin levels are essential. Routine platelet counts may be omitted provided the skin mucous membranes are inspected for haemorrhagic phenomena.

Mutagenicity and carcinogenicity

LEUKERAN 2 mg has been shown to cause chromatid or chromosome damage in man. Acute secondary haematologic malignancies (including leukaemia and myelodysplastic syndrome) have been reported, particularly after long term treatment.

A comparison of patients with ovarian cancer, who received alkylating medicines with those who did not, showed that the use of alkylating medicines, including LEUKERAN 2 mg, significantly increased the incidence of acute leukaemia.

Acute myelogenous leukaemia has been reported in a small proportion of patients receiving LEUKERAN 2 mg 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 2 mg.

Although bone marrow suppression frequently occurs, it is usually reversible if LEUKERAN 2 mg is withdrawn early enough.

Patients with a history of seizure disorder may be particularly susceptible. However irreversible bone marrow failure has been reported.

Severe interstitial pulmonary fibrosis has been reported in patients with chronic lymphocytic leukaemia on long term LEUKERAN 2 mg therapy. Pulmonary fibrosis may not be reversible on withdrawal of LEUKERAN 2 mg.

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

Special populations

Renal impairment

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

Hepatic impairment

Patients with hepatic impairment should be closely monitored for signs and symptoms of toxicity. Since chlorambucil, as in LEUKERAN 2 mg, is primarily metabolised in the liver, dose reduction should be considered in patients with clinically relevant hepatic impairment.

Elderly patients

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, medicine dosage should be titrated carefully in older patients, usually initiating therapy at the low end of the dosage range. The greater frequency of decreased hepatic, renal, and/or cardiac function and of concomitant disease and therapy observed in the elderly also should be considered.

Chlorambucil, as in LEUKERAN 2 mg, has been shown to cause chromosomal damage in humans. Both reversible and permanent sterility have been observed in both sexes (see section 4.6).

Excipients

Lactose warning

LEUKERAN 2 mg contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency,

glucose-galactose malabsorption or fructose intolerance should not take LEUKERAN 2 mg.

4.5. Interaction with other medicines and other forms of interaction

Vaccinations with live organisms: are contraindicated in patients receiving LEUKERAN 2 mg (see section 4.3).

Purine nucleoside analogues (such as fludarabine and cladribine): increased the cytotoxicity of chlorambucil *ex vivo*; however, the clinical significance of this finding is unknown.

4.6. Fertility, pregnancy and lactation

The use of LEUKERAN 2 mg is contraindicated in pregnancy and lactation (see section 4.3). LEUKERAN 2 mg is teratogenic in animals.

Pregnancy

Adequate contraceptive precautions should be advised when either partner is receiving LEUKERAN 2 mg.

Breastfeeding

Mothers receiving LEUKERAN 2 mg should not breastfeed their babies.

Fertility

The overall pubertal development appears to progress normally in females who received chlorambucil, as in LEUKERAN 2 mg, before puberty; however, potential effects on ovarian function remain to be evaluated. LEUKERAN 2 mg may cause

suppression of ovarian function and amenorrhoea has been reported following LEUKERAN 2 mg therapy.

Chlorambucil, as in LEUKERAN 2 mg has been shown to cause chromosomal damage in humans. Both reversible and permanent sterility have been observed in both sexes (see section 4.4).

Azoospermia may be permanent in adult males. Men treated with LEUKERAN 2 mg should be informed about sperm preservation prior to treatment (see sections 4.4 and 4.8)

4.7. Effects on ability to drive and use machines

LEUKERAN 2 mg has a moderate to major influence on a patients' ability to drive and/or use machinery.

Since adverse reactions such as convulsions, movement disorders including tremor, muscle twitching, peripheral neuropathy and myoclonia in the absence of convulsions have been reported in patients receiving LEUKERAN 2 mg, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that LEUKERAN 2 mg does not adversely affect their ability to do so (see section 4.8).

4.8. Undesirable effects

a) Tabulated list of adverse reactions

b) Description of selected adverse reactions

Pancytopenia and irreversible bone marrow depression can occur particularly when the total dosage for the course approaches 6,5 mg/kg in once course therapy with continuous dosing regimen.

In children with nephrotic syndrome, seizures occurred 6 to 90 days after beginning treatment with chlorambucil, as in LEUKERAN 2 mg, in a dosage of 0,2 to 0,7 mg/kg.

Gastrointestinal disorders have been observed when LEUKERAN 2 mg is administered as a single dose of 20 mg or more.

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 providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9. Overdose

Symptoms

Reversible pancytopaenia was the main finding of inadvertent overdoses of chlorambucil, as in LEUKERAN 2 mg.

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 agents

ATC code: L01AA02

Mechanism of action

Chlorambucil is an aromatic nitrogen mustard derivative that acts as a bifunctional alkylating medicine. It has the pharmacological properties of the nitrogen mustard compounds. Chlorambucil is only partly radiomimetric, affecting chiefly the lymphoid tissues. As an alkylating medicine, chlorambucil interferes with DNA replication and transcription of RNA, and ultimately results in the disruption of nucleic acid function.

In vitro studies have shown that the major metabolite of chlorambucil, phenylacetic acid mustard (PAAM), which is also a bifunctional alkylating compound, has antineoplastic activity against some neoplastic human cell lines that is approximately equal to that of chlorambucil. Therefore, the major metabolite of chlorambucil may contribute to the *in vivo* anti-tumour activity

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

medicines and their metabolites via various multi-resistant proteins, alterations in the kinetics of the DNA cross-links formed by these medicines 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 (P-glycoprotein) are substrates of MRP1 (ABCC1) and MRP2 (ABCC2).

5.2. Pharmacokinetic properties

Absorption

Chlorambucil is rapidly absorbed from the gastrointestinal tract following oral administration and is reported to have a terminal half-life of approximately 1,5 hours. The bioavailability of oral chlorambucil is greater than 70 % following administration of single doses of 10 mg to 200 mg. In a limited number of patients administered approximately 0,2 mg/kg of oral chlorambucil, the mean dose adjusted maximum plasma concentration (492 nanograms/ml) occurred between 0,83 and 1,9 hours after administration.

The inter-individual variability in the plasma pharmacokinetics of chlorambucil following oral dosages of between 15 mg and 70 mg was 2-fold for intra-patient variability, and 2 to 4-fold for interpatient variability in AUC).

The absorption of chlorambucil is reduced by food. In a study of ten patients, food intake increased the median time to reach C_{max} two-fold, reduced the peak plasma concentration by greater than 50 % and reduced mean AUC (0-∞) by approximately 27 %.

Distribution

Chlorambucil has a volume of distribution of approximately 0,14 L/kg to 0,24 L/kg. Chlorambucil and its metabolites are extensively protein bound. Chlorambucil covalently binds to plasma proteins, primarily to albumin, 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 has a slightly longer plasma half-life of approximately 2,5 hours. PAAM has similar alkylating activity to Chlorambucil. Chlorambucil and PAAM degrade *in vivo* forming monohydroxy and dihydroxy derivatives. Chlorambucil is not metabolised by cytochrome CYP3A4.

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 1,9 hours.

Elimination

The terminal phase elimination half-life is approximately 1,5 hours for chlorambucil and is 1,8 to 2,5 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Colloidal anhydrous silica, hypromellose, lactose anhydrous, microcrystalline cellulose, polyethylene glycol, stearic acid, synthetic red iron oxide (C.I. 77491), synthetic yellow iron oxide (C.I. 77492), titanium dioxide (C.I. 77891)

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months

6.4. Special precautions for storage

Store between 2 °C to 8 °C.

Keep in original packaging until required for use.

6.5. Nature and contents of container

25 or 50 tablets are packed into a round, amber glass bottle with a child-resistant cap, composed of an inner polypropylene shell and an outer white high-density polypropylene shell. The bottle is placed in an outer cardboard carton.

Not all packs and pack sizes are necessarily marketed.

6.6. Special precautions for disposal

No special requirements.

The handling of LEUKERAN 2 mg should follow guidelines for the handling of cytotoxic medicines according to prevailing local recommendations and/or regulations.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

H2747 (Act 101/1965)

9. DATE OF FIRST AUTHORISATION

Old medicine

10. DATE OF REVISION OF TEXT

01 April 2021

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