IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Leukeran 2 mg film-coated tablets
Chlorambucil
PA1691/007/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Leukeran 2 mg film-coated tablets, from Aspen Pharma Trading Limited for the treatment of:
- Hodgkin's disease;
- Certain forms of non-Hodgkin's lymphoma;
- Chronic lymphocytic leukaemia;
- Waldenstrom's macroglobulinaemia.

is approvable.

The HPRA granted a national marketing authorisation granted in 1979.

This application concerns a mutual recognition procedure with Ireland acting as Reference Member State and Spain as the Concerned Member State. It is bibliographic, submitted under article 10a of Directive 2001/83/EC as amended, so called well-established medicinal use.

As this is an oncology medicine, the product is prescription only which may not be Renewed and to be prescribed by a specialist.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Leukeran 2 mg film-coated tablets
Name(s) of the active substance(s) (INN)	Chlorambucil
Pharmacotherapeutic classification (ATC code)	L01AA02
Pharmaceutical form and strength(s)	Film-coated tablet; 2 mg
Marketing Authorisation Number(s) in Ireland (PA)	PA1691/007/001
Marketing Authorisation Holder	Aspen Pharma Trading Limited
MRP/DCP No.	IE/H/0557/001/MR
Reference Member State	IE
Concerned Member State	ES

II. QUALITY ASPECTS

II.1. Introduction

This application is for Leukeran 2 mg film-coated tablets.

II.2 Drug substance

The active substance is Chlorambucil, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.7 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.8 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical and Pharmaceutical Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Leukeran 2 mg film-coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of chlorambucil are well known. As chlorambucil is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate. A brief summary of the literature submitted is provided below.

Reference is made to the published scientific literature in the Non-Clinical Overview but the GLP status of these studies cannot be assumed or verified.

III.2 Pharmacology

The pharmacology of chlorambucil is well known. Chlorambucil is a nitrogen mustard cytotoxic alkylating agent with a long history of use in the treatment of neoplastic disease. Chlorambucil is a bifunctional alkylating agent that forms DNA cross links, which inhibit replication in proliferating cells. The major metabolite of chlorambucil, phenylacetic acid mustard, is also a bifunctional alkylating agent which contributes to the anti-tumour effect of the drug. Chlorambucil is cytotoxic, its reactivity with DNA, RNA and proteins can cause cell death, resulting in significant adverse effects including tissue toxicity and secondary

malignancies, likely due to induced genetic damage. Hematotoxic effect such as lymphoctopenia and profound bone marrow depletion are also reported in rats.

III.3 Pharmacokinetics

Chlorambucil is rapidly absorbed following oral administration in rats and is generally concentrated in the plasma, as active uptake into the tissues does not occur. However, chlorambucil is highly lipophilic and a weak acid, therefore it can be taken up into cells by passive diffusion, with the highest tissue concentrations present in kidney and liver tissues in the rat. Chlorambucil and its metabolites are extensively bound to plasma and tissue proteins, 99.6% plasma-protein-bound in the rat. Chlorambucil is extensively and rapidly metabolised in the rat with less than 1% chlorambucil, and its major metabolite phenylacetic acid mustard, excreted in the urine in 24 hours. The major metabolite of chlorambucil, phenylacetic acid mustard, is also a bifunctional alkylating agent which contributes to the anti-tumour effect of the drug and may be a more active anti-tumour agent. Enhanced chlorambucil-related toxicity associated with co-administration of the anti-inflammatory agent, phenylbutazone, was demonstrated in mice. This is due to displacement of alkylating agent bound to serum proteins, resulting in enhanced cytotoxicity.

III.4 Toxicology

As with other cytotoxic agents, chlorambucil is mutagenic in *in vitro* and *in vivo* genotoxicity tests and carcinogenic via a genotoxic mechanism. Appropriate warnings regarding the mutagenicity and carcinogenicity of chlorambucil are included in section 4.4 and 5.3 of the SmPC to address this issue.

Non-clinical reproductive and developmental toxicity data from the literature indicate that chlorambucil is embryolethal and teratogenic in rats with evidence of toxicity to fertility. Chlorambucil may cause suppression of ovarian function and amenorrhoea has been reported following chlorambucil therapy. In rats, chlorambucil has been shown to damage spermatogenesis and cause testicular atrophy. Furthermore, 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. Hence, chlorambucil may be teratogenic and should not be used in pregnancy, particularly in the first trimester. Adequate contraceptive precautions should be advised when either partner is receiving Leukeran, and partners should be informed of the drugs effect on germ cells. Also, lactating mothers receiving Leukeran should not breast-feed. Appropriate information is included in sections 4.6 and 5.3 of the SmPC regarding these toxicities.

III.5 Ecotoxicity/environmental risk assessment

The active substance, chlorambucil has a PECsurfacewater below the action limit of 0.01 µg/ml, calculated using a revised Fpen based on disease prevalence data. In addition, a logKow of 1.7 is reported, indicating that chlorambucil is not a PBT substance. Considering the data, Leukeran is not expected to pose a risk to the environment.

III.6 Discussion on the non-clinical aspects

As chlorambucil is a well-known active substances, this is a bibliographic application with no new non-clinical studies conducted by the applicant. The submitted overview of the available non-clinical pharmacodynamic, pharmacokinetic and toxicological data is acceptable. Non-clinical literature data indicate significant toxicities associated with chlorambucil, including genotoxicity, carcinogenicity, embryolethality, teratogenicity and effects on fertility. These toxicities are associated with the mechanism of action of the product and relevant information is included in sections 4.4, 4.6 and 5.3 of the SmPCs. There are no recent non-clinical studies raising safety concerns not previously identified.

IV. CLINICAL ASPECTS

IV.1 Introduction

Chlorambucil is a well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the MR procedure is in accordance with the currently authorised national product Leukeran by Aspen.

The grounds and evidence used for demonstrating that the constituents of chlorambucil have a well-established use with an acceptable level of safety and efficacy is acceptable. The current document summarises the results of chlorambucil clinical studies published since the original regulatory approval.

In relation to GCP, the application is based on published literature data; no new studies specific to this product application are included in the dossier.

IV.2 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 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 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 Cmax 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 (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.

IV.3 Pharmacodynamics

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.

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).

IV.4 Clinical Efficacy

Chlorambucil (CLB) is indicated in the treatment of Hodgkin's disease (HD), certain forms of non-Hodgkin's lymphoma, chronic lymphocytic leukaemia (CLL) and Waldenstrom's macroglobulinaemia (WM). The product has been authorised in Ireland since 1979 and naturally, clinical practice has evolved since then.

The applicant presented data from 54 clinical trials published in the scientific literature (up to November 2014) relating to the efficacy of CLB in treatment of these indications, whether alone or in combination chemotherapy regimens and whether in achievement of complete remission, progression or event free survival and/or overall survival. Clinical studies, up to and including randomised controlled clinical trials, were cited in support of efficacy of CLB and the refinement over time and scientific evolution to current indications. The applicant provided a thorough discussion of this literature and efficacy in the proposed indications is deemed supported.

IV.5 Clinical Safety

The safety profile of chlorambucil is well known and established with a toxicity profile that is clinically acceptable in light of its mechanism of action and patient profile.

The safety profile of chlorambucil is well defined and supported by many decades of post-marketing experience of its use as an oral antineoplastic agent, when used as indicated and at the recommended dose.

The applicant cites 20 clinical studies providing safety data on the use of CLB in HD, Follicular Lyphoma & Mantle Cell Lymphoma, MALT Lymphoma, WM and CLL.

Chlorambucil is authorised for administration as a single agent or as a component of combination chemotherapy. Bone marrow suppression, expected from the pharmacological action of the drug, is the dose limiting toxicity. The main non-haematological toxicities are gastrointestinal and infection (secondary to bone marrow suppression); lung toxicity and peripheral neuropath have also been reported.

Risk management plan (RMP)
The marketing authorisation holder (MAH) has submitted a risk management plan in accordance with the requirements of Directive 2001/83/EC as amended. A summary of the safety concerns for the solution for infusion as approved in the RMP is provided below:

Summary of safety concerns for injection	
Important identified risks	Secondary haematologic malignancies Bone Marrow Suppression Interstitial pulmonary fibrosis, interstitial pneumonia
Important potential risks	Reproductive toxicity, including teratogenicity
Missing information	Use in hepatic-impaired patients Use during breastfeeding Long term safety data in children

Routine pharmacovigilance is considered sufficient to identify and characterise the risks of the product.
Routine risk minimisation measures are sufficient to minimise the risks of the product

in the proposed indication.

The applicant references the last periodic safety update report (PSUR) for CLB (22 June 2013 to 21 June 2014) which uses the number of CLB tablets sold worldwide as an alternative measure to patient exposure, due to variation in CLB dosage regimens for various indications. The estimated cumulative number of CLB tablets sold worldwide in the reference period is 606.7 million 2 mg tablets and 136 million 5 mg tablets. No new safety issues were identified to result in changes to the Reference Safety Information; the applicant concludes that the safety profile of CLB is adequately reflected in the reference safety information. The next PSUR submission date on the EURD List for CLB is 13 December 2025, a submission frequency interval of 13 years.

With regard to PSUR submission, the MAH should take the following into account:

PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.

For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV.6 Discussion on the clinical aspects

As the use of chlorambucil is well established and supported by many publications over the years concerning both its safety and efficacy, no new clinical studies to evaluate the benefit/risk balance were submitted by the applicant. Instead, reference is made to the provided scientific literature.

The overall benefit risk for this product from a clinical perspective is positive. No potential serious risk to public health has been identified. This is a well-established product from a safety & efficacy perspective.

V. OVERALL CONCLUSIONS

As the use of chlorambucil is well established and supported by many publications over the years concerning both its safety and efficacy, no new clinical studies to evaluate the benefit/risk balance were submitted by the applicant. Instead, reference is made to the provided scientific literature.

The literature presented supports the authorised indications and the known safety and efficacy profile. In view of the morbidity and mortality of the authorised indications there are no absolute contraindications except use in non-malignant disease and hypersensitivity to the active substance.

The Applicant reports chlorambucil remains under study in clinical trials to ascertain its benefit alongside new agents, given its favourable toxicity profile compared to other antineoplastic agents, particularly in the elderly and/or those unfit for new standard treatment regimens.

The overall benefit risk for this product from a clinical perspective is positive. No potential serious risk to public health has been identified. This is a well-established product from a safety & efficacy perspective.

In view of the life threatening nature and associated morbidity of the authorised indications, it is concluded that oral CLB, when used as indicated and at the recommended dose, continues to have a positive benefit/risk ratio in the treatment of:

- Hodgkin's disease,
- Certain forms of non-Hodgkin's lymphoma,
- Chronic lymphocytic leukaemia and

- Waldenstrom's macroglobulinaemia.

In light of the type of application and longevity of its license in Ireland, the product is approvable.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

VI. REVISION DATE

The marketing authorisation has been granted unlimited validity in the RMS.