IPAR

Public Assessment Report for a Medicinal Product for Human Use

Scientific Discussion

Alkeran 50mg, Powder and Solvent for Solution for Infusion
Melphalan
Melphalan
PA1691/004/001

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.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Alkeran, in the treatment of multiple myeloma, melanoma & soft tissue sarcoma, advanced ovarian carcinoma, advanced neuroblastoma, polycythaemia rubra vera and breast carcinoma is approvable. A national marketing authorisation was 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.

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	Alkeran 50 mg, Powder and Solvent for Solution for Infusion & Alkeran 2 mg Film-coated Tablets
Name(s) of the active substance(s) (INN)	MELPHALAN
Pharmacotherapeutic classification (ATC code)	L01AA03 Nitrogen mustard analogues
Pharmaceutical form and strength(s)	50 mg, Powder and Solvent for Solution for Infusion & 2 mg Film-coated Tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA1691/004/001-2
Marketing Authorisation Holder	Aspen Pharma Trading Limited
MRP/DCP No.	IE/H/0558/001-002/MR
Reference Member State	IE
Concerned Member State	ES

II. QUALITY ASPECTS

II.1. Introduction

This application is for Alkeran 50 mg, Powder and Solvent for Solution for Infusion & Alkeran 2 mg Film-coated Tablets.

II.2 Drug substance

The active substance is Melphalan, 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

Composition of the medicinal product - Alkeran 50 mg, Powder and Solvent for Solution for Infusion contains 50 mg of Melphalan and Alkeran 2 mg Film-coated Tablets contains 2 mg of Melphalan.

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

Both Alkeran 50 mg, Powder and Solvent for Solution for Infusion and Alkeran 2 mg Film-coated Tablets are established pharmaceutical forms and they 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 processes for both products have been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

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 for Alkeran 50 mg, Powder and Solvent for Solution for Infusion is based on the pharmacopoeial monograph for Parenteral preparations and for Alkeran 2 mg Film-coated Tablets the Finished Product

Specification is based on the pharmacopoeial monograph for Tablets. The tests and control limits are considered appropriate for this type of products.

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 products of consistent quality.

P.6 Packaging material

The approved packaging for both products is described in section 6.5 of the SPCs.

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

P.7 Stability of the Finished Product

Stability data on the finished products 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 SPCs.

II.4 Discussion on Chemical, Pharmaceutical and Biological 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 Alkeran 50 mg, Powder and Solvent for Solution for Infusion and Alkeran 2 mg Film-coated Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This application for a marketing authorisation was submitted in accordance with Article 10a of Directive 2001/83/EC as amended, a well-established use application. Melphalan has been in well-established use within the European Union for more than ten years, demonstrating a recognised efficacy and safety profile. A non-clinical overview has been provided, it is based on relevant published literature and written by an appropriately qualified person.

III.2 Pharmacology

The pharmacology of melphalan is well known and well described in the literature. No new non-clinical studies have been conducted by the applicant in support of this

application, and none are required. A non-clinical overview of the literature has been provided. Melphalan is a nitrogen mustard which acts as a non-specific DNA alkylating agent that creates bifunctional adducts with cross-links in DNA, resulting in cytotoxic action. Melphalan also reduces Interlukin-6 protein expression, contributing to the inhibition of malignant cell growth.

III.3 Pharmacokinetics

The pharmacokinetics of melphalan is well known and well described in the literature. No new non-clinical studies have been conducted by the applicant in support of this application, and none are required. The overview supplied is sufficient.

III.4 Toxicology

No new non-clinical toxicity studies have been submitted. The toxicity profile of melphalan is well characterised in the published literature indicating toxicity to reproduction, teratogenic, mutagenic and carcinogenic effects.

III.5 Ecotoxicity/environmental risk assessment

The applicant had committed to revising the PEC surface water in accordance with the Guideline for the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2*) as a follow-up measure.

III.6 Discussion on the non-clinical aspects

Melphalan has been in well-established use within the European Union for more than 10 years, demonstrating a recognised efficacy and safety profile. An abridged dossier was submitted in accordance with Article 10a of Council Directive 2001/83/EEC as amended. No new nonclinical studies were submitted. The non-clinical evidence in support of this application is based on relevant published scientific literature which is appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

Melphalan 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 Alkeran.

The main clinical overview provided, version March 2015 (CCDS version 19) provides a critical analysis of the clinical data published on melphalan based on a literature search with a publication cut-off date of 15th July 2014.
Since then there have been 2 addendums to the clinical overview:
Version April 2016 – update to company core datasheet (CCDS version 20)
Version July 2017 – update to CCDS version 21 regarding thromboembolic events from combination therapy and increased risk of solid tumour second primary malignancies (SPM)

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

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

The absorption of oral melphalan from the GI tract is highly variable with respect to both the time to first appearance of the drug in plasma and peak plasma concentration. In studies of the absolute bioavailability of melphalan the mean absolute bioavailability ranged from 56 to 85%. Melphalan is moderately bound to plasma proteins with reported percent binding ranging from 69% to 78%. About 10% of the drug is excreted unchanged in the urine within 9 days of oral administration. Approximately 20-50% of the dose is eliminated via faeces. Melphalan is eliminated by both renal excretion and spontaneous chemical degradation to its mono- and di-hydroxy metabolites. The latter pathway is a relatively minor contributor (<5%) because plasma protein binding retards the hydrolysis rate of Melphalan, being likely the renal excretion the major elimination pathway for Melphalan.

IV.3 Pharmacodynamics

Melphalan is a nitrogen mustard alkylating agent. Alkylation through covalent binding with the 7-nitrogen of guanine on DNA, cross-linking two DNA strands prevents cell replication. Alkylating agents react extensively with cellular macromolecules, such as DNA, RNA and proteins, and thus induce multiple kinds of molecular lesions. Melphalan is known to undergo an intramolecular nucleophilic substitution reaction to produce an aziridinium ion. Another mechanism of action noted is cellular apoptosis via the mitochondrial and p53 pathway.

IV.4 Clinical Efficacy

Melphalan is indicated for the treatment of multiple myeloma, advanced ovarian adenocarcinoma, advanced neuroblastoma, cutaneous melanoma, soft tissue

sarcoma, advanced breast cancer & polycythaemia rubra vera. The product was first license was in Ireland in 1979 and naturally clinical practice has evolved since then. The indications reflect the time the product was initially licensed. Melphalan is effective when administered intravenously or orally as an option for management of multiple myeloma and advanced neuroblastoma in the paediatric setting. The NCCN guidelines for advanced ovarian carcinoma lists melphalan as a therapeutic option in the recurrent setting. Melphalan can be used when administered by regional arterial perfusion in the management of cutaneous malignant melanoma and soft tissue sarcoma.

IV.5 Clinical Safety

The safety profile of melphalan is well known and established with a toxicity profile that is clinically acceptable in light of its mechanism of action and patient profile. Depending on the indication, the most common adverse drug reactions are haematological and gastrointestinal toxicities. The main toxicities associated with HDM therapy with ASCT are myelosuppression, infection and mucositis. No potential serious risk to public health has been identified.

Risk management plan (RMP)

The 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 powder and solvent for solution for infusion	
Important identified risks	Myelosuppression Reproductive toxicity Haematological malignancies Interstitial lung disease and pulmonary fibrosis Veno-occlusive disease (VOD)
Important potential risks	Venous thromboembolism (VTE) Teratogenicity Solid second primary malignancies
Missing information	Use in paediatric population Use in elderly

The summary of safety concerns for the tablets is below:

Summary of safety concerns for tablets	
Important identified risks	Myelosuppression

	Reproductive toxicity Haematological malignancies Interstitial lung disease and pulmonary fibrosis
Important potential risks	Venous thromboembolism (VTE) Teratogenicity Solid second primary malignancies
Missing information	Use in paediatric population Use in elderly

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.

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 melphalan 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 melphalan 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. While all the indications listed do not reflect current clinical practice, 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.