COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Melfalanhydrochloride SUN 50 mg powder and solvent for solution for injection/infusion

(melphalan hydrochloride)

NL/H/3954/001/DC

Date: 15 November 2018

This module reflects the scientific discussion for the approval of Melfalanhydrochloride SUN 50 mg powder and solvent for solution for injection/infusion. The procedure was finalised on 24 April 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Melfalanhydrochloride SUN 50 mg powder and solvent for solution for injection/infusion, from Sun Pharmaceutical Industries Europe B.V.

- The product, at conventional intravenous dosage, is indicated in the treatment of multiple myeloma and advanced ovarian cancer.
- The product, at high intravenous dosage, is indicated, with or without haematopoietic stem cell transplantation, for the treatment of multiple myeloma and childhood neuroblastoma.
- The product, administered by regional arterial perfusion, is indicated in the treatment of localized malignant melanoma of the extremities and localized soft tissue sarcoma of the extremities.

In the above indications, melphalan may be used alone or in combination with other cytotoxic drugs.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Alkeran 50 mg Infusion, powder and solvent for solution for infusion (NL RVG 6690) which has been registered in the Netherlands by Aspen Pharma Trading Limited since 18 April 1973.

The concerned member states (CMS) involved in this procedure were Germany, France, Italy, Sweden and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

<u>Orphan similarity</u>

An orphan similarity assessment is submitted, taking into account the following products:

- For the treatment of multiple myeloma: Ninlaro, Revlimid, Kyprolis, Darzalex, Farydak, Imnovid, Thalidomide Celgene.
- For the treatment of ovarian cancer: Lynparza, Yondelis, Zejula.
- For the treatment of childhood neuroblastoma: Dinituximab beta Apeiron.
- For the treatment of localised soft tissues sarcoma of the extremities: Yondelis, Lartruvo.

The MAH concludes that “Mephalan SUN vs Revlimid, Thalidomide Celgene, Ninlaro (Ixazomib),Farydak, Kyprolis, Lynparza, Yondelis, Dinutuximab Beta Aperion, Lartruvo, Zejula and Darzalex are not similar. Upon comparison all these products were considered to be non similar based on the mechanism of action and the principal molecular structure.

II. QUALITY ASPECTS

II.1 Introduction

- Melfalanhydrochloride SUN powder for solution for injection/infusion is a white to off-white freeze-dried powder of cake
- Melfalanhydrochloride SUN solvent for solution for injection/infusion is a clear colourless liquid/solution.

Each vial of powder contain melphalan hydrochloride equivalent to 50 mg melphalan. After reconstitution with 10 ml of the solvent, the resultant solution contains 5 mg/ml melphalan. The pH of the reconstituted solution is 6.5.

The powder and solvent for solution for injection/infusion are packed in a clear, glass vial with a bromobutyl rubber stopper and aluminium collar with a plastic flip-top cover

The excipients are:
Powder – hydrochloric acid and povidone
Solvent – water for injection, sodium citrate, propylene glycol and ethanol

II.2 Drug Substance

The active substance is melphalan hydrochloride, an established active substance. There is a European Pharmacopoeia (Ph.Eur.) monograph on melphalan, however not being the hydrochloride salt. The hydrochloride salt is a white to off-white powder. It is slightly soluble in methanol and alcohol. It is not reported in literature that the active substance shows polymorphism. The anhydrous crystalline form is produced consistently.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

<u>Manufacturing process</u>
The manufacturing steps are adequately described. The starting materials are acceptable and sufficiently described. The controls on critical steps, in-process controls and controls on intermediates are considered adequate.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. The assay and related substances method have been adopted from the Ph.Eur. monograph of melphalan. The other tests are in-house methods. The ASMF-holder applies impurity specifications from the monograph and in addition two in-house specifications for certain impurities. All other proposed drug substance specifications are considered acceptable. Batch analytical data demonstrating compliance with this specification have been provided for multiple batches.

Stability of drug substance

Stability data on the active substance have been provided for 3 batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The batches were stored in accordance with applicable European guidelines. All available long-term and accelerated results are meeting the set requirements. Based on the data submitted, a retest period could be granted of 36 months when stored between 15˚C and 30˚C.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.
The development is strongly based on the qualitative and quantitative composition of the reference medicinal product. In view of the close resemblance to the innovator product, the good compatibility between the drug substance and the chosen excipients can be expected. A batch with the proposed formulation of the lyophilised product is very comparable to the innovator product regarding description, related substances, water content, reconstitution time, pH of reconstituted solution and chloride content.
Temperature cycling studies have demonstrated that the proposed product can withstand the effects of high and low temperature variations that may be encountered during shipping and handling and there will be no impact on quality of the drug product.
pH exposure studies did not reveal large impact on the pH of the final reconstituted solution, and also in stability studies pH values between 6.33 and 6.62 were measures in inverted orientation without affecting the quality of the product. The critical process parameters have been identified and evaluated before being optimised in further development studies. In the comparability testing similar data were obtained for 3 batches of the proposed product and one batch of the innovator product. Overall, the development of the medicinal product is acceptable.

Manufacturing process

The manufacturing process has been adequately described and validated according to relevant European guidelines. The process consists of ten steps such as preparation, sterilisation, filtration, washing, depryogenationa and filling of the vials, freeze drying and inspection. The in-process controls are considered acceptable. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients
For all excipients Ph. Eur. requirements are applied. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, pH of reconstituted solution, constitution time, uniformity of dosage units (weight variation), clarity of solution, particulate matter of reconstituted solution, assay, related substances, water content, uniformity of mass, bacterial endotoxins, and sterility. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for 3 batches of both the powder product and the diluent product stored at 25°C/60% RH (9 months) and 40°C/75% RH (6 months). A photostability study showed that the product is light sensitive.
On basis of the data submitted, a shelf life was granted of 2 years. The product should not be stored above 30°C or refrigerated. The vial should be kept in the outer carton in order to protect from light. Chemical and physical in use stability have been demonstrated for 1 hour at room temperature. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are responsibility of user. Any unused portion should be discarded.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Melfalanhydrochloride SUN has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Melfalanhydrochloride SUN is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Alkeran which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Melfalan hydrochloride is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Melfalanhydrochloride SUN 50 mg powder and solvent for solution for injection/infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Melfalanhydrochloride SUN is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Melfalanhydrochloride SUN.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Mutagenicity - Tumour lysis syndrome

	- Malignancy
Important potential risks	- Gastrointestinal toxicities including haemorrhagic enterocolitis when used in combination with Nalidixic acid - Decreased clearance in patients with renal impairment
Missing information	- Use in elderly patients

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Alkeran. No new clinical studies were conducted. The MAH demonstrated that the quantitative composition of the product is similar to the quantitative composition of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Melfalanhydrochloride SUN 50 mg powder and solvent for solution for injection/infusion have a proven chemical-pharmaceutical quality and are generic forms of Alkeran 50 mg Infusion, powder and solvent for solution for infusion. Alkeran is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted,

considered that essential similarity has been demonstrated for Melfalanhydrochloride SUN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 24 April 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/3954/1/IA/001	Replacement or addition of a manufacturer responsible for importation and/or batch release; including batch control/testing	-	22-11-2018	Approved	-