COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Melfalan Amarox 50 mg, powder and solvent for solution for injection/infusion

(melphalan hydrochloride)

NL/H/5086/001/DC

Date: 29 November 2021

This module reflects the scientific discussion for the approval of Melfalan Amarox 50 mg, powder and solvent for solution for injection/infusion. The procedure was finalised at 15 July 2021. 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 Melfalan Amarox 50 mg, powder and solvent for solution for injection/infusion, from Amarox Pharma B.V.

The product is indicated for:

- localised malignant melanoma of the extremities;
- localised sarcoma of the soft tissues of the extremities.

Melfalan Amarox can be used in conventional intravenous doses in the treatment of:

- multiple myeloma: either as monotherapy or in combination with other cytotoxic agents;
- advanced ovarian cancer on its own or in combination with other cytotoxic agents (see section 5.1 of the SmPC).

Melfalan Amarox can be used in high intravenous doses in the treatment of:

- multiple myeloma (see section 5.1 of the SmPC);
- advanced neuroblastoma in children (see section 5.1 of the SmPC).

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 powder and solvent for solution for injection/infusion (NL RVG 06690) which has been registered in the Netherlands since 13 April 1973, currently by MAH Aspen Pharma Trading Limited.

The concerned member states (CMS) involved in this procedure were Germany and Spain.

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

<u>Orphan similarity assessment</u>

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

- For the treatment of multiple myeloma: Ninlaro (ixazomib), Kyprolis (carfilzomib), Farydak (panobinostat), Imnovid (pomalidomide), Darzalex (daratumumab), Blenrep (belantamab mafodotin).
- For the treatment of ovarian cancer: Zejula (niraparib).
- For the treatment of childhood neuroblastoma: Qarziba (dinutuximab beta).

In view of the above comparisons, it can be concluded that none of the approved products in the EU/EEA with a valid orphan designation are similar to Melfalan Amarox, within the meaning of Article 3 of Commission Regulation (EC) No. 847, as one or more of the three

criteria for assessing similarity (molecular structural features, mechanism of action and therapeutic indication) are not fulfilled.

II. QUALITY ASPECTS

II.1 Introduction

Melfalan Amarox consists of a powder and a solution. The powder is a white to off white cake or powder. The solvent is a clear, colourless solution (10 ml). The pH of the reconstituted solution is 6.0 to 7.0.

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

The powder is packed in a clear, type I glass vial with flurotec laminated rubber stopper and aluminium with a flip off seal.
The solvent is packed in a clear, type I glass vial with flurotec laminated rubber stopper and aluminium with a flip off seal.

The excipients are:
Powder - povidone K12 and hydrochloric acid (for pH adjustment)
Solvent - ethanol, (96%), sodium citrate anhydrous, propylene glycol and water (for injections).

II.2 Drug Substance

The active substance is melphalan hydrochloride, an established active substance not described in any Pharmacopoeia as hydrochloride salt. There is a European Pharmacopoeia (Ph. Eur.) monograph on melphalan (i.e. not the hydrochloride salt). The active substance melphalan hydrochloride is a white to off-white powder. It is slightly soluble in methanol and alcohol. Melphalan hydrochloride polymorphism is not reported in literature.

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.

Manufacturing process

The manufacturer of melphalan hydrochloride performs two synthesis steps, a purification step and a salt formation step, from the intermediate to the final drug substance. This intermediate is produced by another manufacturer, via three full chemical steps. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of in-house methods and of the monograph for melphalan (i.e. not the hydrochloride salt) in the Ph. Eur. It is considered acceptable to apply these monograph specifications for the impurities for the melphalan hydrochloride substance. The specific optical rotation requirement for melphalan hydrochloride is different from that of the monograph for melphalan. The identification tests are considered acceptable. The test parameters on bacterial endotoxins and microbiological purity are included. All analytical methods have been fully described, and the quantitative methods have been sufficiently validated. The specifications for melphalan hydrochloride as applied by the ASMF-holder and drug product manufacturer are identical. Batch analytical data demonstrating compliance with the specification have been provided for four batches. The controls on critical steps, in-process controls and controls on intermediates are considered adequate.

Stability of drug substance

Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines demonstrating the stability of the active substance at 25°C/60% RH (24 months) and at 40°C/75% RH (six months). 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 in the original package in order to protect from moisture, oxygen and light. Excursions in temperature are allowed 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. In general, the development of this generic product is strongly based on the qualitative and quantitative composition of the reference medicinal product. During the development risk assessment is applied based on a Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQA) of the drug product, including initial and final assessments of CQAs and their justification. This is also done for the solvent product. The risks for the drug substance attributes, microbial contamination and bacterial endotoxins content were evaluated and justified.

In view of the close resemblance to the innovator product, the good compatibility between the drug substance and the chosen excipients can be expected. It was remarked that the quantity of hydrochloric acid is amended compared to the innovator product, because

melphalan is used in the innovator product and in the proposed product melphalan hydrochloride. In the final reconstituted solution the resulting pH is approximately the same. Further, the MAH has performed temperature cycling studies, lyophilisation cycle development studies, dissolution studies, a process components compatibility study, a lab-scale stability study and a photostability study. The photostability study demonstrated that the drug product was light sensitive.

The MAH also provided comparability testing data for three batches of the test product and one batch of the reference product including data on the reconstituted product and the diluted product to the infusion solution. The behaviour of the test product was confirmed to be the same as the reference product after reconstitution and further dilution. In addition, the compatibility of the infusion solution with PVC and non-PVC infusion sets was tested. The in-use data for both types of infusion sets are fully comparable and confirm compatibility. The comparability testing data form the basis for justification of the biowaiver, which will be discussed in section IV.

Manufacturing process

The MAH provided a full description of the manufacturing process with all involved steps. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

The excipients of both the powder and the solvent meet the specifications in the corresponding Ph. Eur. monographs. These specifications are acceptable.

Microbiological attributes

For both the powder product as well as the diluent product terminal sterilisation is applied. Three diluent product batches have been terminally sterilised and batch analysis results were meeting the set requirements. Further, the MAH adequately addressed the integrity of the container closure system. Bacterial immersion testing was performed on the drug product in media filled vials.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification for the powder comprises tests that are usual for a powder for solution for infusion. These specification includes tests for appearance, identification, pH of reconstituted solution, colour absorbance, clarity of solution, reconstitution time, water determination, uniformity of dosage units, assay of melphalan, related substances, particulate matter of reconstituted solution (visible and subvisible particles), assay, bacterial endotoxins and sterility. For the solvent, the specification includes tests for appearance, identification, acidity or alkalinity, sodium citrate content, ethanol content, particulate matter (visible and subvisible particles), bacterial endotoxins, sterility, extractable volume and viscosity. Limits in the specifications for both the powder and solvent have been justified and are considered appropriate for adequate quality control of the product. A risk evaluation

on elemental impurities has been performed in line with ICH Q3D for both the powder product as well as the diluent product. There are no risks on elemental impurities and specific controls are no further needed.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site on three batches of both the powder and solvent have been provided, demonstrating compliance with the specifications.

Stability of drug product

Stability data on the product have been provided for three batches of both the powder and solvent in accordance with applicable European guidelines demonstrating the stability of the product at 25°C/60% RH, 30°C/65% RH and at 40°C/75% RH for six months. In the accelerated studies the assay contents slightly decreased, however, the total impurities increase was only limited. In one batch, out-of-specification results for any unspecified impurity were found at three and six months in the study under accelerated conditions. Further, for both the powder and the solvent product the accelerated, intermediate and long-term results do meet the set specifications and no other significant changes have been observed. According to the provided photostability results, light does have an impact on the quality of the product.

On basis of the data submitted, a shelf life was granted of two years. After reconstitution and dilution, chemical and physical stability has been demonstrated for 1 hour and 15 minutes at 25°C. Therefore the total time from reconstitution and dilution to the completion of infusion should not exceed 1 hour and 15 minutes. The labelled storage conditions are: 'Do not store above 30°C. Do not refrigerate. Keep the vial in the outer carton in order to protect from light.'

From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. The reconstituted solution should not be refrigerated as this will cause precipitation.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Melfalan Amarox 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 Melfalan Amarox 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 50 mg powder and solvent for solution for injection/infusion 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

Melphalan 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. The MAH applied for a waiver for a bioequivalence study, which is discussed in the next paragraph.

IV.2 Pharmacokinetics

Biowaiver

Melfalan Amarox 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 comparability testing data confirmed that the behaviour of the test product is the same as that of the reference product after reconstitution and further dilution. Therefore, it may be considered as

therapeutic equivalent, with the same efficacy and 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 Melfalan Amarox.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• None
Important potential risks	• None
Missing information	• None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient to identify, characterise, prevent or minimise risks.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Alkeran 50 mg powder and solvent for solution for injection/infusion. No new clinical studies were conducted. Since both the reference and current product are intended for parenteral use, no bioequivalence study was needed to show that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. A biowaiver has been granted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Melfalan Tillomed 50 mg powder and solvent for solution for injection/infusion for content and key safety messages, and to Levetiracetam Hetero 750 mg Film-Coated Tablets for design and layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Melfalan Amarox 50 mg, powder and solvent for solution for injection/infusion has a proven chemical-pharmaceutical quality and is a generic form of Alkeran 50 mg powder and solvent for solution for injection/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 was deemed necessary. A biowaiver has been granted.

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 Melfalan Amarox with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 July 2021.

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