LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Melphalan Pharmexon
(melphalan hydrochloride)

SE/H/1796/01/DC

This module reflects the scientific discussion for the approval of Melphalan Pharmexon. The procedure was finalised on 2019-03-13. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Melphalan Pharmexon, 50 mg, Powder and solvent for solution for injection/infusion, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Pharmexon Consulting s.r.o, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, BE, BG, CZ, DK, FI, HR, HU, IE, LT, LV, NL, NO, PL, PT, RO, SI and SK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Alkeran, 50 mg, Powder and solvent for solution for injection/infusion authorised in NL since 1973, with Aspen Pharma Trading Limited as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS AT, BG, DK, FI, HR, HU, LT, LV, NL, NO, PL, PT, RO and SI: Alkeran, 50 mg, Powder and solvent for solution for injection/infusion, authorised in NL since 1973, with Aspen Pharma Trading Limited as marketing authorisation holder.
The justification to use this product is based on information received from NL.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Melphalan Pharmexon is intended for intravenous use and regional arterial perfusion only.
The applied product contains the same active substance in the same concentration as the currently authorised product and the same excipients in similar amounts. None of the excipients are known to interact with the drug substance. For this type of product, no bioequivalence studies are required according to the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1).

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

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 Melphalan Pharmexon.

Safety specification submitted by the applicant:

Table 2: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Malignancy • • Mutagenicity • Tumour lysis syndrome
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

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed

Summary of the RMP
The submitted Risk Management Plan, version 0.2 signed 26 Oct 2018 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

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 language used for the purpose of user testing the PIL was English.

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

The quality of the generic product, Melphalan Pharmexon, is found adequate. There are no objections to approval of Melphalan Pharmexon, from a non-clinical and clinical point of view. The product information is acceptable.

It should be noted that an updated Annex to the EC Guideline on "Excipients in the labelling and package leaflet of medicinal products for human use" was published in March 2018. While this document has been considered in the RMS assessment and in the proposals for SmPC changes, the recommendation regarding restricted use due to in children aged 5 years or less due, to *propylene glycol content*, has not been implemented. The reason is that, according to current European recommendations (SIOPEN), busulfan and melphalan should be considered standard high-dose chemotherapy for high-risk neuroblastoma also in children below 5 years of age (Ladenstein et al, Lancet Oncol 2017 Apr;18(4):500-514. doi: 10.1016/S1470-2045(17)30070-0). Thus, the B/R for melphalan is deemed positive also for this population.

The benefit/risk ratio is considered positive and Melphalan Pharmexon, 50 mg, Powder and solvent for solution for injection/infusion, is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Melphalan Pharmexon, 50 mg, Powder and solvent for solution for injection/infusion, was positively finalised on 20190313.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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