IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Plerixafor Seacross 20 mg/ml solution for injection
Plerixafor
PA22766/007/001

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 HPRA has granted a marketing authorisation for Plerixafor Seacross 20mg/ml Solution for Injection, from Seacross Pharma (Europe) Ltd on 31st March 2023 for:

Adult patients: combination with granulocyte-colony stimulating factor (G-CSF) to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in adult patients with lymphoma or multiple myeloma whose cells mobilise poorly.
Paediatric patients (1 to less than 18 years): combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in children with lymphoma or solid malignant tumours, either:

- pre-emptively, when circulating stem cell count on the predicted day of collection after adequate mobilization with G-CSF (with or without chemotherapy) is expected to be insufficient with regards to desired hematopoietic stem cells yield, or

who previously failed to collect sufficient haematopoietic stem cells.

The reference product in IE is Mozobil 20 mg/ml solution for injection
MAH: Genzyme Europe B.V.
Date of authorisation: 2009-07-31
The legal basis for this submission is article 10.1 so called 'generic application'.

According to the regulatory requirements CPMP/EWP/QWP/1401/98 NfG on the Investigation of Bioavailability and Bioequivalence, a bioequivalence study is not required for parenteral aqueous solutions and the applicant has not submitted any.

With IE as the Reference Member State and CZ, DE, DK, EE, ES, FI, FR, HR, HU, IT, LT, NL, NO, PL,PT, RO, SE, SI, and SK as Concerned Member States in this Decentralized Procedure, Seacross Pharma (Europe) Ltd is applying for the Marketing Authorisation for Plerixafor Seacross 20 mg/ml Solution for injection.

Name of the product	Plerixafor Seacross 20mg/ml Solution for Injection
Name(s) of the active substance(s) (INN)	Plerixafor
Pharmacotherapeutic classification (ATC code)	L03AX16
Pharmaceutical form and strength(s)	20mg/ml Solution for Injection
Marketing Authorisation Number(s) in Ireland (PA)	PA22766/007/001
Marketing Authorisation Holder	Seacross Pharma (Europe) Ltd
MRP/DCP No.	IE/H/1193/001/DC
Reference Member State	IE
Concerned Member State	CZ DE DK EE ES FI FR HR HU IT LT NL NO PL PT RO SE SI SK

II. QUALITY ASPECTS

II.1. Introduction

This application is for Plerixafor Seacross 20mg/ml Solution for Injection.

II.2 Drug substance

The active substance is plerixafor an established active substance not described in the European/British 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

One ml of solution contains 20 mg plerixafor. Each vial contains 24 mg plerixafor in 1.2 ml solution.

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/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 is based on the pharmacopoeial monograph for the dosage form, 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.6 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.7 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, 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 Plerixafor 20mg/ml Solution for Injection.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This finished product is a generic formulation of Mozobil 20 mg/ml solution for injection on the European market. No new preclinical data have been submitted. This is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment

Since Plerixafor Seacross 20 mg/ml Solution for Injection is intended for generic substitution, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary. An appropriate justification for the absence of studies was provided by the applicant.

III.3 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of plerixafor are well known. As plerixafor 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. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

IV. CLINICAL ASPECTS

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

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Mozobil 20 mg/ml solution for injection Genzyme Europe B.V.

According to the regulatory requirements CPMP/EWP/QWP/1401/98 NfG on the Investigation of Bioavailability and Bioequivalence, a bioequivalence study is not required for parenteral aqueous solutions and the applicant has not submitted any.

IV.2 Pharmacokinetics

No new pharmacokinetic data has been provided. The following is from the SmPC.

The pharmacokinetics of plerixafor have been evaluated in lymphoma and multiple myeloma patients at the clinical dose level of 0.24 mg/kg following pre-treatment with G-CSF (10 µg/kg once daily for 4 consecutive days).

Absorption

Plerixafor is rapidly absorbed following subcutaneous injection, reaching peak concentrations in approximately 30-60 minutes (tmax). Following subcutaneous administration of a 0.24 mg/kg dose to patients after receiving 4-days of G-CSF pre-treatment, the maximal plasma concentration (Cmax) and systemic exposure (AUC0-24) of plerixafor were 887 ± 217 ng/ml and 4337 ± 922 ng·hr/ml, respectively.

Distribution

Plerixafor is moderately bound to human plasma proteins up to 58%. The apparent volume of distribution of plerixafor in humans is 0.3 l/kg demonstrating that plerixafor is largely confined to, but not limited to, the extravascular fluid space.

Biotransformation

Plerixafor is not metabolised in vitro using human liver microsomes or human primary hepatocytes and does not exhibit inhibitory activity in vitro towards the major drug-metabolising CYP450 enzymes (1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5). In in vitro studies with human hepatocytes, plerixafor does not induce CYP1A2, CYP2B6, and CYP3A4 enzymes. These findings suggest that plerixafor has a low potential for involvement in P450-dependent drug-drug interactions.

Elimination

The major route of elimination of plerixafor is urinary. Following a 0.24 mg/kg dose in healthy volunteers with normal renal function, approximately 70% of the dose was excreted unchanged in urine during the first 24 hours following administration. The elimination half-life (t1/2) in plasma is 3-5 hours. Plerixafor did not act as a substrate or inhibitor of P-glycoprotein in an in vitro study with MDCKII and MDCKII-MDR1 cell models.

IV.3 Pharmacodynamics

No new pharmacodynamic data was submitted as part of this application.

In pharmacodynamic studies in healthy volunteers of plerixafor alone, peak mobilisation of CD34+ cells was observed from 6 to 9 hours after administration. In pharmacodynamic studies in healthy volunteers of plerixafor in conjunction with G-CSF administered at identical dose regimen to that in studies in patients, a sustained elevation in the peripheral blood CD34+ count was observed from 4 to 18 hours after plerixafor administration with peak response between 10 and 14 hours.

In order to compare the pharmacokinetics and pharmacodynamics of plerixafor following 0.24 mg/kg based and fixed (20 mg) doses, a trial was conducted in adult patients with NHL (N=61) who were treated with 0.24 mg/kg or 20 mg of plerixafor. The trial was conducted in patients weighing 70 kg or less (median: 63.7 kg, min: 34.2 kg, max: 70 kg). The fixed 20 mg dose showed 1.43-fold higher exposure (AUC0-10h) than the 0.24 mg/kg dose (Table 2). The fixed 20 mg dose also showed numerically higher response rate (5.2% [60.0% vs 54.8%] based on the local lab data and 11.7% [63.3% vs 51.6%] based on the central lab data) in attaining the target of ≥ 5 × 106 CD34+ cells/kg than the mg/kg-based dose. The median time to reach ≥ 5 ×106 CD34+ cells/kg was 3 days for both treatment groups, and the safety profile between the groups was similar. Body weight of 83 kg was selected as the cut-off point to transition patients from fixed to weight based dosing (83 kg x 0.24 mg = 19.92 mg/kg).

IV.4 Clinical Efficacy
No new efficacy data was submitted.

IV.5 Clinical Safety
No new safety data was submitted.

Special populations
Renal impairment
Following a single dose of 0.24 mg/kg plerixafor, clearance was reduced in subjects with varying degrees of renal impairment and was positively correlated with creatinine clearance (CrCl). Mean values of AUC0-24 of plerixafor in subjects with mild (CrCl 51-80 ml/min), moderate (CrCl 31-50 ml/min) and severe (CrCl ≤ 30 ml/min) renal impairment were 5410, 6780, and 6990 ng.hr/ml, respectively, which were higher than the exposure observed in healthy subjects with normal renal function (5070 ng·hr/ml). Renal impairment had no effect on Cmax.

Gender
A population pharmacokinetic analysis showed no effect of gender on pharmacokinetics of plerixafor.

Elderly
A population pharmacokinetic analysis showed no effect of age on pharmacokinetics of plerixafor.

Paediatric population
The pharmacokinetics of plerixafor were evaluated in 48 paediatric patients (1 to less than 18 years) with solid tumours at subcutaneous doses of 0.16, 0.24 and 0.32 mg/kg with standard mobilisation (G- CSF plus or minus chemotherapy). Based on population pharmacokinetic modeling and similar to adults, µg/kg-based dosage results in increase in plerixafor exposure with increasing body weight in paediatric patients. At the same weight-based dosing regimen of 240 µg/kg, the plerixafor mean exposure (AUC0-24h) is lower in paediatric patients aged 2 to <6 years (1410 ng.h/mL), 6 to <12 years (2318 ng.h/mL), and 12 to <18 years (2981 ng.h/mL) than in adults (4337 ng.h/mL). Based on population pharmacokinetic modeling, the plerixafor mean exposures (AUC0-24h) in paediatric patients aged 2 to <6 years (1905 ng.h/mL), 6 to <12 years (3063 ng.h/mL), and 12 to <18 years (4015 ng.h/mL), at the dose of 320 µg/kg are closer to the exposure in adults receiving 240 µg/kg. However, mobilization of PB CD34+ count was observed in stage 2 of the trial.

IV.6 Discussion on the clinical aspects
The application contained an adequate review of published clinical data and bioequivalence is not required as this is a parenteral product.

V. OVERALL CONCLUSIONS

The benefit risk of plerixafor is considered positive.

VI. REVISION DATE

05.02.2028