IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Cyclophosphamide Seacross 1000 mg powder for solution for injection/infusion
Cyclophosphamide monohydrate
PA22766/013/003

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 HPRA has granted a marketing authorisation for Cyclophosphamide Seacross 200 mg, 500 mg, 1000 mg and 2000 mg powder for solution for injection/ infusion, from Seacross Pharma (Europe) Limited on 6th December 2024 for the treatment of:

- Chronic Lymphocytic Leukaemia (CLL),
- Acute Lymphocytic Leukaemia (ALL),
- As conditioning for a bone marrow transplantation, in the treatment of Acute Lymphoblastic Leukaemia, Chronic Myelogenous Leukaemia and Acute Myelogenous Leukaemia in combination with whole body irradiation or busulfan,
- Hodgkin's lymphoma, Non-Hodgkin's lymphoma and Multiple Myeloma,
- Metastatic ovarian and breast, carcinoma,
- Adjuvant treatment of breast carcinoma,
- Ewing's sarcoma,
- Small cell lung cancer,
- advanced or metastatic neuroblastoma,
- Life-threatening autoimmune diseases: severe progressive forms of lupus nephritis and Wegener's granulomatosis. This application for a marketing authorisation was submitted in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as a 'generic' application. With Ireland as the Reference Member State in this decentralised procedure, Seacross Pharma (Europe) Limited applied for a marketing authorisation for Cyclophosphamide 200 mg, 500 mg, 1000 mg and 2000 mg powder for solution for injection/infusion in Ireland, Germany (all strengths), Spain (500 mg, 1000 mg), France (500 mg, 1000 mg), Italy (500 mg, 1000 mg), the Netherlands (500 mg, 1000 mg, 2000 mg) and Portugal (500 mg, 1000 mg). The reference product was Endoxana Injection, MAH: Baxter Holding B.V. The legal status for this marketing authorisation is subject to medical prescription, 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	Cyclophosphamide Seacross 200 mg, 500 mg, 1000 mg and 2000 mg powder for solution for injection/ infusion
Name(s) of the active substance(s) (INN)	Cyclophosphamide monohydrate
Pharmacotherapeutic classification (ATC code)	L01AA01
Pharmaceutical form and strength(s)	Powder for solution for injection/infusion
Marketing Authorisation Number(s) in Ireland (PA)	PA22766/013/001; PA22766/013/002; PA22766/013/003; PA22766/013/004.
Marketing Authorisation Holder	Seacross Pharma (Europe) Limited
MRP/DCP No.	IE/H/1277/001-004/DC
Reference Member State	Ireland
Concerned Member State	DE; ES; FR; IT; NL; PT.

II. QUALITY ASPECTS

II.1. Introduction

This application is for Cyclophosphamide Seacross 200 mg, 500 mg, 1000 mg and 2000 mg powder for solution for injection/ infusion

II.2 Drug substance

The active substance is cyclophosphamide monohydrate, 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

Each vial Cyclophosphamide Seacross 200 mg, powder for solution for injection/infusion contains 213.8 mg cyclophosphamide monohydrate equivalent to 200 mg cyclophosphamide.

Each vial Cyclophosphamide Seacross 500 mg, powder for solution for injection/infusion contains 534.5 mg cyclophosphamide monohydrate equivalent to 500 mg cyclophosphamide.

Each via Cyclophosphamide Seacross 1000 mg, powder for solution for injection/infusion contains 1069.0 mg cyclophosphamide monohydrate equivalent to 1000 mg cyclophosphamide.

Each vial Cyclophosphamide Seacross 2000 mg, powder for solution for injection/infusion contains 2138.0 mg cyclophosphamide monohydrate equivalent to 2000 mg cyclophosphamide.

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.7 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.8 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 Cyclophosphamide Seacross 200 mg, 500 mg, 1000 mg and 2000 mg powder for solution for injection/ infusion.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Endoxan I.V. on the European market. No new preclinical data have been submitted. This is acceptable for this type of application.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since Cyclophosphamide 200 mg, 500 mg, 1 g and 2 g powder for solution for injection/infusion is a generic product, it will not lead to an increased exposure to the environment. Further studies on environmental risk assessment are therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of cyclophosphamide are well known. As cyclophosphamide is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. A nonclinical overview based on literature review was provided and is acceptable for this type of generic application. Nonclinical sections of the SmPC are acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

Cyclophosphamide 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 Endoxana Injection marketed by Baxter Holding B.V..

At the time of administration, this product is an aqueous solution administered by injection or infusion. No pharmacokinetic studies are required to support this application. This is based on the fact that the product is an aqueous intravenous solution containing the same active substance as the reference product as outlined in the Guideline on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/Corr **.

IV.2 Pharmacokinetics

<u>Absorption</u>
Cyclophosphamide is quickly and almost completely absorbed from parenteral sites.

<u>Distribution</u>

Less than 20% of cyclophosphamide is bound to plasma proteins. The protein binding of the metabolites of cyclophosphamide is higher but less than 70%. To what extent the active metabolites protein bound, is not known.

Cyclophosphamide is about in the cerebrospinal fluid and the mother's milk. Cyclophosphamide and metabolites can pass through the placenta.

Metabolism
Cyclophosphamide is activated in the liver to the active metabolites 4-hydroxy-cyclophosphamide and aldofosfamide (tautomeric form of 4-hydroxy-cyclophosphamide) through phase I metabolism by cytochrome P450 (CYP) enzymes. Different CYP isozymes contribute to the bioactivation of cyclophosphamide, including CYP2A6, 2B6, 2C9, 2C19 and 3A4, 2B6 in which the exhibits highest 4-hydroxylase activity. Detoxification is done mainly through glutathione-S-transferases (GSTA1, GSTP1) and alcohol dehydrogenase (ALDH1, ALDH3). Two to four hours after administration of cyclophosphamide, the plasma concentrations of the active metabolites are maximal, after which a rapid decrease of plasma concentrations takes place.

Elimination
The plasma half-life of cyclophosphamide is about 4 to 8 hours in adults and children. The plasma half-lives of the active metabolites are not known.

Following high-dose IV administration within the framework of allogeneic bone marrow transplantation, the plasma concentration of pure cyclophosphamide follows linear first- order kinetics. Compared with conventional cyclophosphamide therapy, there is an increase in inactive metabolites, indicating saturation of activating enzyme systems, but not of the stages of metabolism leading to inactive metabolites. During the course of high-dose cyclophosphamide therapy over several days, there is a decrease in the areas under the plasma concentration-time curve of the parent compound, probably due to auto-induction of microsomal metabolism activity.

Cyclophosphamide and its metabolites are primarily excreted by the kidneys.

IV.3 Pharmacodynamics

Cyclophosphamide is an inactive prodrug requiring enzymatic activation. Cyclophosphamide when administered, rapidly metabolises into 4-hydro-cyclophosphamide in the presence of cytochrome P450 isoenzyme and co-exists with its tautomer, aldophosphamide. Aldophosphamide further interacts with aldehyde dehydrogenase and forms carboxy-cyclophosphamide. Aldophosphamide decomposes into phosphoramide mustard and acrolein. Phosphoramide is an active neoplastic agent which acts on seven guanine residues of DNA, whereas acrolein is a toxic metabolite that causes toxicity in the myocardium, cardiofibroblasts and endothelial cells.

The immunosuppressive effect of cyclophosphamide is based on the fact that cyclophosphamide has an inhibitory effect on B-cells, CD4 + T-cells and to a lesser extent on CD8 +-T-cells. In addition, it is assumed that cyclophosphamide has an inhibitory effect on the suppressor that regulate the IgG2 class of antibodies.

IV.4 Clinical Efficacy

No new clinical studies were completed which is acceptable for an abridged/generic application.

IV.5 Clinical Safety

No new clinical studies were completed which is acceptable for an abridged/generic application.

Risk Management Plan

The submitted Risk Management Plan, version 0.2 signed 01/02/2024 is considered acceptable.

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

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.

Periodic Safety Update Report (PSUR)

Active substance is currently listed in the published EURD list

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.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

Cyclophosphamide Seacross 200 mg, 500 mg, 1000 mg and 2000 mg powder for solution for injection/infusion has a proven chemical-pharmaceutical quality and is a generic form of a suitable approved reference product. Cyclophosphamide Seacross 200 mg, 500 mg, 1000 mg and 2000 mg powder for solution for injection/infusion is a well-known medicinal product with an established favourable efficacy and safety profile. No clinical studies or bioequivalence/bioavailability studies are considered necessary.

V. OVERALL CONCLUSIONS

Cyclophosphamide Seacross 200 mg, 500 mg, 1000 mg and 2000 mg powder for solution for injection/infusion is a generic form of Endoxana Injection marketed by Baxter Holding B.V., which is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, based on the data submitted considered that Cyclophosphamide Seacross 200 mg, 500 mg, 1000 mg and 2000 mg powder for solution for injection/infusion has
a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

23.10.2029