COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Cyclofosfamide Accord 2000 mg, powder for solution for injection / infusion (cyclophosphamide)

NL/H/5257/001/DC

Date: 19 January 2022

This module reflects the scientific discussion for the approval of Cyclofosfamide Accord 2000 mg, powder for solution for injection / infusion. The procedure was finalised at 20 October 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

ALL	Acute Lymphocytic Leukemia
ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CLL	Chronic Lymphocytic Leukemia
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
ERP	European Reference Product
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 Cyclofosfamide Accord 2000 mg, powder for solution for injection / infusion, from Accord Healthcare B.V.

Cyclophosphamide is used in combination with chemotherapy regimens or alone, depending on the indication. The product is indicated in the treatment of:

- Chronic Lymphocytic Leukemia (CLL)
- Acute Lymphocytic Leukemia (ALL)
- As conditioning for a bone marrow transplantation, in the treatment of Acute Lymphocytic Leukaemia, Chronic myelogenous leukaemia and Acute myelogenous leukaemia in combination with whole body irradiation or busulfan
- Hodgkin's disease, Non-Hodgkin's lymphoma and Multiple Myeloma
- Metastatic ovarian and breast, carcinoma
- Adjuvant treatment of breast carcinoma
- Ewing's sarcoma
- Small cell lung cancer
- Advances or metastatic neuroblastoma
- Life-threatening autoimmune diseases: severe progressive forms of lupus nephritis and Wegener's granulomatosis.

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 European reference product (ERP) Endoxan I.V., powder for solution for injection (lyophilisate) 2000 mg, by Baxter B.V. In the Netherlands, Endoxan I.V. has been registered since 22 October 1981 (RVG 08058). The justification to use this product is based on RMS's own files.

The concerned member states (CMS) involved in this procedure were Austria, Croatia, Germany, Slovakia and United Kingdom (Northern Ireland).

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

Similarity assessment in view of the orphan drug legislation

The MAH provided a similarity report in which potential similarity between Cyclofosfamide Accord 2000 mg, powder for solution for injection / infusion and authorised orphan medicinal products under market exclusivity, was discussed.

As for the therapeutic indication, the MAH described the designated orphan conditions for which there is an overlap with the indications of cyclophosphamide per authorised orphan

medicinal product: Zejula, Qarziba, Soliris, Iclusig, Blincyto, Besponsa, Xaluprine, Kymriah, Imbruvica, Gazyvaro, Adcetris, Dacogen, Mylotarg, Xospata, Vyxeos liposomal, Rydapt, Daurismo, Yescarta, Ledaga, Poteligeo and Polivy. The MAH stated that there is an overlap with indications of approved orphan medicinal products. However, the orphan medicinal products are mostly targeted therapies licensed for specific target populations in terms of biomarkers and/or line of treatment, whereas cyclophosphamide is licensed for multiple indications encompassing a broad target population. This is agreed. Further, the MAH stated that all of the orphan medicinal products harbour a different mechanism of action, as most of them are targeted treatment products. The mode of action of Ledaga resembles that of cyclophosphamide, but differs in mechanism of action. It is only approved for topical treatment of mycosis fungoides-subtype cutaneous T-cell lymphoma, while cyclophosphamide is a systemic administered drug which has to be activated into alkylating substances by the liver. Also, the MAH stated that the chemical structures of the medicinal products listed in Table 1 are different, compared to Cyclofosfamide Accord.

Table 1: Summary table of medicinal product under evaluation and authorised orphan medicinal product(s): tailed similarity report

Active Substance	Disease / condition	Date of decision	Decision	Medicine name
Niraparib	Ovarian cancer	16/11/2017	Positive	Zejula
Dinutuximab beta	Neuroblastoma	05/05/2017	Positive	Qarziba
Ponatinib	Acute lymphoblastic leukaemia	01/07/2013	Positive	Iclusig
	Treatment of chronic myeloid leukaemia	01/07/2013	Positive	
Blinatumomab	Acute lymphoblastic leukaemia	23/11/2015	Positive	Blincyto
Inotuzumab ozogamicin	Acute lymphoblastic leukaemia	29/06/2017	Positive	BESPONSA
Mercaptopurine	Acute lymphoblastic leukaemia	09/03/2012	Positive	Xaluprine
Tisagenlecleucel	Acute lymphoblastic leukaemia	22/08/2018	Positive	Kymriah
Ibrutinib	Treatment of chronic lymphocytic leukaemia	21/10/2014	Positive	Imbruvica
Obinutuzumab	Treatment of chronic lymphocytic leukaemia	22/07/2014	Positive	Gazyvaro
Brentuximab vedotin	Treatment of Hodgkin lymphoma	30/10/2012	Positive	Adectris
Decitabine	Treatment of acute myeloid leukaemia	20/09/2012	Positive	Dacogen
Gemtuzumab Ozogamicin	Treatment of acute myeloid leukaemia	19/04/2018	Positive	Mylotarg
Gilteritinib	Treatment of acute myeloid leukaemia	24/10/2019	Positive	Xospata
Liposomal combination of cytarabine and daunorubicin	Treatment of acute myeloid leukaemia	23/08/2018	Positive	Vyxeos liposomal
Midostaurin	Treatment of acute myeloid leukaemia	20/09/2017	Positive	Rydapt

Ixazomib citrate	Treatment of multiple myeloma	27/09/2011	Positive	Ninlaro
Carfilzomib	Treatment of multiple myeloma	03/06/2008	Positive	Kyprolis
Belantamab mafodotin	Treatment of multiple myeloma	16/10/2017	Positive	Blenrep
Panobinostat lactate anhydrous	Treatment of multiple myeloma	08/11/2012	Positive	Farydak
Pomalidomide	Treatment of multiple myeloma	08/10/2009	Positive	Imnovid
Idecabtagene vicleucel	Treatment of multiple myeloma	19/08/2021	Positive	Abecma
Glasdegib maleate	Treatment of acute myeloid leukaemia	16/10/2017	Positive	Daurismo
Daratumumab	Treatment of plasma cell myeloma	24/05/2016	Positive	Darzalex

Having considered the arguments presented by the MAH and with reference to article 8 of Regulation (EC) No 141/2000, Cyclofosfamide Accord 2000 mg, powder for solution for injection / infusion is considered not similar (as defined in article 3 of Commission Regulation (EC) No. 847/2000) to the products listed in Table 1 and therefore the existence of any market exclusivity for any of these product will not prevent the granting of the marketing authorisation of Cyclofosfamide Accord.

II. QUALITY ASPECTS

II.1 Introduction

Cyclofosfamide Accord is a white lyophilised powder or cake. The powder is packed in glass vials. Each vial contains 2138.0 mg cyclophosphamide monohydrate equivalent to 2000 mg of cyclophosphamide. The strength after reconstitution is 20 mg cyclophosphamide (anhydrous)/ml solution. The excipient is mannitol (E421).

The excipients and packaging are usual for this type of dosage form.

II.2 Drug Substance

The active substance is cyclophosphamide, an established active substance described in the European Pharmacopoeia (Ph. Eur.). The active substance is a white or almost white crystalline powder, which is freely soluble in ethanol and soluble in water. Cyclophosphamide monohydrate exhibits isomerism, it is a racemic mixture.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph. Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph. Eur and the additional requirements of the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three full scaled batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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 choice of excipients is justified, and their functions explained. The main development studies were the characterisation of the reference product, formulation development and manufacturing process development.
The MAH investigated the similarity of the product's formulation with the formulation of two reference products: Endoxan 500 mg/vial and 1 g/vial (MAH: Baxter Oncology GmbH, Germany) and Cyclophosphamide Injection 500 mg/vial and 1 g/vial (MAH: Baxter Healthcare Ltd, United Kingdom). However, these data could only be seen as supportive as these strengths were not part of the submitted dossier. Further, the MAH provided a comparison between the product and one United States reference product batch. The proposed composition was considered quantitative and qualitative similar in regards to the active substance and qualitative similar in relation to the excipient (mannitol) of the reference product. No further data were requested, as this concerns a parenteral product for intravenous administration. From a quality point of view, the proposed drug product with mannitol and the both reference products used during development without mannitol are considered similar. Moreover, it is noted that the innovator product Endoxan I.V. (RVG 08058) also contains mannitol.

Overall, the drug development was appropriately performed and described.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. The manufacturing process consists of the following steps: dispensing of raw material, manufacturing of bulk solution, preparation of filtration equipment/assembly, pre-filtration of bulk solution, container closure preparation, filling and half stoppering, freeze

drying, sealing, leak test & external vial washing and inspection, labelling and packaging. The manufacturing process has been described in sufficient detail.
As the drug product is manufactured using a sterile filtration / aseptic filling process, the manufacturing process is regarded nonstandard. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three full scale batches.

Control of excipients
The excipients comply with the Ph. Eur. requirements. 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 description, identification, pH of reconstituted solution, clarity of reconstituted solution, uniformity of dosage units, colour of reconstituted solution, organic impurities, assay, bacterial endotoxins, sterility, particulate contamination, water and reconstitution time. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Moreover, the MAH provided a risk evaluation concerning the presence of nitrosamine impurities in the product in question and applying the principles outlined in the notice "Information on nitrosamines for marketing authorisation holders (EMA/189634/2019)".

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data on three full scale 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 three production scaled batches stored at 5 = 5ºC ± 3ºC (18 months) and 25ºC ± 2ºC/60% ± 5%RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in a clear moulded glass vial stoppered with grey Westar rubber stopper and aluminium flip-off seal. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.
Out-of-specification results were observed for the cyclophosphamide ring open dimer impurity in two out of three batches of the 1 g/vial strength under accelerated conditions. Under long term conditions, no significant changes or trends were observed for any of the investigated parameters.

Based on the stability data submitted, a shelf-life was granted of 18 months. The labelled storage conditions (also after reconstitution / dilution) are: 'Store in a refrigerator (2°C - 8°C)'. At these conditions, in-use stability of the reconstituted and diluted solution has been demonstrated for 48 hours. From a microbiological point of view, the medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24

hours at 2°C - 8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

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 Cyclofosfamide Accord has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Cyclofosfamide Accord 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 Endoxan I.V. 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

Cyclophosphamide 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. Also, since the product is

to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorised reference product, there was no need to submit a bioequivalence study.

IV.2 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 Cyclofosfamide Accord.

Table 2. 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 for the risks and areas of missing information.

IV.3 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Endoxan. No new clinical studies were conducted. 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 multiple bridging report making reference to Cyclofosfamide Sandoz 500 mg, 1000 mg and 2000 mg, powder for solution for injection/infusion for the key safety messages (NL/H/2977/001-003/DC). For design and layout, reference was made to Levitracetam 250/500/750/1000 mg film-coated tablets (EMEA/H/C/002290). 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

Cyclofosfamide Accord 2000 mg, powder for solution for injection/ infusion has a proven chemical-pharmaceutical quality and is a generic form of Endoxan I.V., powder for solution

for injection (lyophilisate) 2000 mg. Endoxan I.V. 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 Cyclofosfamide Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 October 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