COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Cyclofosfamide Accord 500 mg and 1000 mg, powder for solution for injection/infusion (cyclophosphamide monohydrate)

NL/H/5098/001-002/DC

Date: 14 January 2022

This module reflects the scientific discussion for the approval of Cyclofosfamide Accord 500 mg and 1000 mg, powder for solution for injection/infusion. The procedure was finalised at 14 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
HPLC	High Performance Liquid Chromatography
ICH	International Conference of Harmonisation
IR	Infrared
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 500 mg and 1000 mg, powder for solution for injection/infusion, from Accord Healthcare B.V.

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

- Chronic Lymphocytic Leukaemia (CLL)
- Acute Lymphocytic Leukaemia (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 innovator products Endoxan I.V., 500 mg and 1000 mg, powder for solution for injection (lyophilisate) (NL License RVG 08058) which have been registered in the Netherlands by Baxter B.V. since 22 October 1981.

The concerned member states (CMS) involved in this procedure were Austria (1000 mg only), Belgium, Bulgaria (500 mg only), Cyprus, Czech Republic, Germany, Denmark, Estonia, Spain (1000 mg only), Finland, France, Croatia (1000 mg only), Hungary, Lithuania, Latvia, Malta, Norway, Poland, Portugal, Sweden, Slovenia, Slovakia and the United Kingdom (Northern Ireland) .

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

Assessment of orphan similarity

The MAH has provided a similarity report in which potential similarity between Cyclofosfamide Accord 500 mg and 1000 mg, powder for solution for injection/infusion and the orphan medicinal products Zegula (niraparib), Qarziba (dinutuximab beta), Soliris (eculizumab), Iclusing (ponatinib), Blincyto (blinatumomab), Besponsa (inotuzumab ozogamicin), Xaluprine (mercaptopurine) and Xaluprine (tisagenlecleucel) for the treatment

of the indicated disease/conditions mentioned in the introduction above. Some of the indications (ovarian cancer, neuroblastoma, myasthenia gravis and acute lymphoblastic leukaemia) overlap with indications of approved orphan medicinal products. However, given the differences in the mechanism action, Cyclofosfamide Accord can be considered as not similar to the currently authorised orphan medicinal products. Therefore, the existence of any market exclusivity for any of these product will not prevent the granting of the marketing authorisation of Cyclofosfamide Accord 500 mg and 1000 mg, powder for solution for injection/infusion.

II. QUALITY ASPECTS

II.1 Introduction

Cyclofosfamide Accord are white lyophilised powders or cakes for solution for injection/infusion.

Each vial of Cyclofosfamide Accord 500 mg, powder for solution for injection/infusion contains 534.5 mg cyclophosphamide monohydrate equivalent to 500 mg cyclophosphamide.
Each vial of Cyclofosfamide Accord 1000 mg, powder for solution for injection/infusion contains 1069.0 mg cyclophosphamide monohydrate equivalent to 1000 mg cyclophosphamide.

For both product strengths, the strength after reconstitution is 20 mg cyclophosphamide (anhydrous) per ml solution.

The powders for solution for injection/infusion are packed in 30 ml (500 mg strength) or 50 ml (1000 mg strength) clear moulded type I glass vials stoppered with grey westar silicon chlorobutyl rubber stopper and an aluminium flip-off seal.

The excipient is mannitol (E421).

II.2 Drug Substance

The active substance is cyclophosphamide monohydrate, 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 specification is based on the Ph. Eur. monograph on cyclophosphamide and the additional requirements of the CEP. The following tests are included: description, solubility, identification, appearance of the solution, pH, water content, limit of chlorides, limit of phosphates, related compounds, assay, residual solvents, nickel content, bacterial endotoxins and microbial limit test. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for three production scaled batches stored at 5°C (60 months) and 25°C/60% RH (six months) in accordance with applicable European guidelines. The batches were stored in double polyethylene bag (inner bag is transparent followed by outer black coloured bag) in a fiberboard drum. The bags are fastened separately with plastic fastener. Based on the data submitted, a retest period could be granted of 60 months when stored in tight and light resistant containers and at 5°C, excursions are permitted between 2˚C and 8˚C.

II.3 Medicinal Products

Pharmaceutical development

The products are established pharmaceutical forms and their 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. Formulation development was confined to investigation of similarity of the MAH's formulation with the formulation of the reference products. Similarity of the MAH's formulation with the formulation of the reference products is claimed based on comparable impurity profile, pH of reconstituted solution, water content and assay. From a quality point of view, the proposed products with mannitol and the reference products used during development without mannitol can be considered similar. Moreover, it is noted that the innovator product Endoxan as registered in the reference member state also contains mannitol. Results of clinical studies or bioequivalence studies are not required and have not been provided.

Manufacturing process

The manufacturing process consists of dispensing of raw material, manufacturing of bulk solution, preparation of filtration, pre-filtration of bulk solution, container closure preparation, filling and half stoppering, freeze drying, sealing, leak test and external vial washing and inspection, labelling and packaging. The manufacturing process has been described in sufficient detail. As the drug product is manufactured using an sterile filtration/aseptic filling process, the manufacturing process is regarded non-standard. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full scale batches of each strength in accordance with the relevant European guidelines.

Control of excipients

The excipient complies with the Ph. Eur. requirements. This specification is acceptable.

Quality control of drug products

The finished products specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, pH of reconstituted solution, clarity of reconstituted solution, uniformity of dosage units, colour of reconstituted solution, impurities, assay, bacterial endotoxins, sterility, particulate contamination, water and reconstitution time. The release and shelf-life limits are identical except for certain related compounds. Limits in the specification have been justified and are considered appropriate for adequate quality control of the products. The analytical methods have been adequately described and validated. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three full scaled batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug products

Stability data on the products have been provided on three production scaled batches per strength stored at 5˚C (24 months (500 mg/vial) and 18 months (1000 mg/vial)) and 25˚C/60% RH (six months) in accordance with ICH stability guidelines. The batches were stored in the proposed packaging. Photostability studies were performed in accordance with ICH recommendations and showed that the products are stable when exposed to light. Out of specification results were observed for a parameter in two out of three batches of the 1000 mg/vial strength at 25˚C/60% RH. At 5˚C, no significant changes or trends were observed for any of the other investigated parameters. On basis of the data submitted, a shelf life was granted of two years. The labelled storage condition is: ‘Store in a refrigerator (2°C – 8˚C).’

Chemical and physical in-use stability of reconstituted solution (concentration 20 mg/ml) and diluted solution (concentration 2 mg/ml) has been demonstrated for 48 hours at 2°C - 8°C.

From a microbiological point of view, the medicinal products 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.

For storage condition after reconstitution/dilution of Cyclofosfamide Accord see section 6.3 of the SmPC.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the products 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 have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished products.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Cyclofosfamide Accord are 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

These products are generic formulations of Endoxan which are available on the European market. Reference is made to the preclinical data obtained with the innovator products. 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 monohydrate 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.

IV.2 Pharmacokinetics

Cyclofosfamide Accord 500 mg and 1000 mg, powder for solution for injection/infusion are parenteral formulations and therefore fulfil 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 quantitative composition of Cyclofosfamide Accord are entirely the same that of the originator products. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current products can be used instead of the reference products.

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 Cyclofosfamide Accord.

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 and minimise risks relating to the products.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator products Endoxan. No new clinical studies were conducted. The products can be considered essentially similar to the reference products based on chemical-pharmaceutical

properties. Risk management is adequately addressed. These generic medicinal products can be used instead of the reference products.

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 Cyclofosfamide Sandoz 500 mg, 1000 mg and 2000 mg, powder for solution for injection/infusion (NL/H/2977/001-003/DC) for content and Levetiracetam 250 mg, 500 mg, 750 mg and 1000 mg film-coated tablets (EMEA/H/C/002290) 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

Cyclofosfamide Accord 500 mg and 1000 mg, powder for solution for injection/infusion have a proven chemical-pharmaceutical quality and are generic forms of Endoxan 500 mg and 1000 mg, powder for solution for injection. Endoxan are well-known medicinal products with established favourable efficacy and safety profiles.

Since both the reference and current products 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 products, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 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