CBG MEB

Public Assessment Report

Scientific discussion

Cyclofosfamide Sandoz 500 mg, 1000 mg and 2000 mg, powder for solution for injection/infusion

(cyclophosphamide)

NL/H/2977/001-003/DC

Date: 29 December 2014

This module reflects the scientific discussion for the approval of Cyclofosfamide Sandoz 500 mg, 1000 mg and 2000 mg, powder for solution for injection/infusion. The procedure was finalised on 23 July 2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Cyclofosfamide Sandoz 500 mg, 1000 mg and 2000 mg, powder for solution for injection/infusion from Sandoz B.V.

Cyclophosphamide may be used alone or in combination with other chemotherapeutic agents, depending on the indication. Cyclophosphamide 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 Lymphoblastic Leukemia, Chronic Myelogenous Leukemia and Acute Myelogenous Leukemia . 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.

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 product Endoxan I.V., 500 mg, 1000 mg, 2000 mg powder for solution for injection (lyophilisate) (NL License RVG 08058) which has been registered in the Netherlands by Baxter B.V. since 22 October 1981.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Croatia, France (only 500 mg & 1000 mg), Germany, Hungary (only 500 mg & 1000 mg), Luxembourg, Malta, Poland, Romania, Spain and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Cyclofosfamide Sandoz is a white crystalline powder. Each vial contains 500 mg, 1000 mg or 2000 mg cyclophosphamide.

500 mg is filled into a 50mL Type I, clear glass vial, sealed with a serum stopper, and secured with a flip-off seal with a red polypropylene plastic button.

1000 mg is filled into a 100mL Type I, clear glass vial, sealed with a serum stopper, and secured with a flip-off seal with a sea green polypropylene plastic button.

2000 mg is filled into a 100mL Type I, clear glass vial, sealed with a serum stopper, and secured with a flip-off seal with a brown yellow polypropylene plastic button.

When reconstituted for intravenous use, all solutions for administration contain 20 mg cyclophosphamide per ml.

The finished product does not contain any excipients.

II.2 Drug Substance

The active substance is cyclophosphamide an established active substance described in the European, British and United States Pharmacopoeia (Ph.Eur., BP, USP). It is a white, crystalline powder which is soluble in water and freely soluble in ethanol. Cyclophosphamide has two isomers. The crystalline form of cyclophosphamide is manufactured.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process consists of two steps, preparation of the crude cyclophosphamide and refinement of cyclophosphamide to obtain a sterile active substance. The proposed starting materials are considered acceptable and acceptable specifications are set. No class I solvents are used. The active substance is adequately characterized. The process is described in sufficient detail.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. monograph and the USP monograph on cyclophosphamide. Most tests and limits are in line with the tests and limits described in the Ph.Eur. monograph on cyclophosphamide. The test for assay and related substance is performed as per USP, which is acceptable considering that the methods and limits described in the USP are more specific and cross-validation is performed. 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-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches of full scale, stored at 25°C/60% RH (12 months) and 30°/65% RH (12 months). The batches were stored in the commercial packaging. No changes were seen in any of the parameters tested at 12 months, stability of the substance at these conditions is shown. The proposed re-test period of 24 months is considered acceptable, the proposed storage condition (Store below 30°C) is also considered acceptable.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described in sufficient detail. The innovator product in the Netherlands, Endoxan, contains mannitol and is manufactured via lyophilisation. For the generic product aseptic filling of the sterile drug substance without excipients is performed. The choice of the sterilisation method is acceptable, because the substance is sensitive to heat.
Equivalence to the reference product has been sufficiently demonstrated. The choices of the packaging and manufacturing process are justified.

Manufacturing process
A description of the process is provided. The main steps are washing of the vials and stoppers and the filling and capping of the product. The manufacturing process is a non-standard process requiring process validation on full scale batches. Process validation data on the product has been presented for three batches of each strength, showing compliance to the acceptance criteria. The manufacturing process has been adequately validated according to relevant European guidelines.

Microbiological attributes

Detailed information on the container closure system, and microbiological attributes is provided Integrity of container closure system for prevention of microbial contamination are sufficiently demonstrated.

Quality control of drug product
The product specification includes tests for appearance, physical evaluation, identification, completeness of solution, constitution time, water, pH, colour and clarity of solution, uniformity of dosage units, visible particles, degradation product, bacterial endotoxins, sterility, and assay. Release and shelf-life limits are the same and acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full-scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on three full-scale batches of each strength stored at 25°C/60% RH (12-18 months) and 30°/65% RH (12 months).
The conditions used in the stability studies are according to the ICH stability guideline; the absence of testing at 40°C is justified. The batches were stored in the commercial packaging, i.e. a type I, clear glass vial, sealed with a serum stopper, and secured with a flip-off seal. The product was demonstrated to be photostable. No changes are noted at any of the conditions, the proposed shelf-life of 24 months is supported. The proposed storage condition 25°C is therefore justified.

Stability data has been provided demonstrating that the product remains stable for 24 hours when diluted with saline and stored at 2-8°C. Additional data on reconstitution and further dilution of the product with Ringer's solution, 5% dextrose, and 0.9% saline have been provided as well.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Cyclofosfamide Sandoz 500 mg, 1000 mg and 2000 mg have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Cyclofosfamide Sandoz 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 tot 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.

IV.2 Pharmacokinetics

Biowaiver
Cyclofosfamide Sandoz 500 mg, 1000 mg and 2000 mg, powder for solution for injection/infusion is a parenteral formulation and therefore fulfils 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 authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). 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 product can be used instead of its reference product.

IV.3 Clinical efficacy and safety

Therapeutic indications
The proposed indications are in line with the approved indications of the reference product in the Netherlands, Endoxan powder for solution for injection.

In addition to the in the RMS already approved indications, the MAH proposed to amend some of the indications upon request of the CMS in order to achieve harmonisation with nationally approved indications:

- The wording of the indications ALL, neuroblastoma and small cell lung cancer was revised to be less specific.
- It was agreed to maintain the indication CML as part of the conditioning for a bone marrow transplantation. The MAH argued that overall in the fist-line and second-line cytotoxic therapy of CM has been substituted by imatinib, desatinib and nilotinib. However, approximately one third of the patient suffering from CML still need another treatment including stem cell transplantation. The addition of 'in combination with whole body irradiation or busulfan' was agreed upon.
- With respect to the non-malignant diseases, one CMS proposed to extend the indication to further auto-immune diseases, like diseases causing inflammation and pain in the joints and autoimmune nephropathy which are resistant to corticosteroids. On the other hand, another CMS requested to restrict the indication and a third member state proposed to delete the indication for autoimmune diseases completely. The MAH provided additional literature references to support the indications for the autoimmune diseases lupus erythematodes and Wegener's granulomatosis. Inclusion of these indications is considered sufficiently justified.
- Although one CMS argued that the indications for cyclophosphamide should be limited to adults, the member states agreed that this medicinal product can be used in adults and children. Cyclophosphamide is among others indicated for the treatment of children with Ewing sarcoma, ALL and neuroblastoma.
- The MAH proposed to list Ewing's sarcoma in a separate line and not in the context of metastatic treatment. This was agreed as cyclophosphamide can be used for the treatment of Ewing's sarcoma also in case of local disease (not metastasized).

Comments which did not lead to revisions were the following:

- Two member states requested to include in the indication Chronic Lymphocytic Leukaemia the words 'after failure of standard therapy (chlorambucil/prednisone)'. The MAH argued that fludarabine is accepted as the most effective single-agent chemotherapy for the treatment of CLL and that cyclophosphamide together with fludarabine play an important role in modern multi-agent regimens which frequently include also monoclonal antibodies. These combination regimens including also cycloposphamide are used in first-line treatment. It was thus agreed that the CLL indication should not be restricted to next line therapy.
- Although one of the CMS proposed addition of the indication vesical cancer, this is not included as there is not sufficient literature available to support the indication.
- Regarding the indications Hodgkin's, non-Hodgkin's and multiple myeloma, it was proposed to add 'remission induction therapy'. Cyclophosphamide is an important constituent in most multi-agent regimens used for the treatment of non-Hodgkins's of any risk group. Moreover, cyclo-phosphamide is also included in the multi-agent regimens that are recommended for the treatment of multiple myeloma and non-Hodgkin's. The MAH therefore argued that the indication should not

be limited to remission induction therapy only. The member states agreed to the conclusion that further specification of the indications Hodgkin's lymphoma, non-Hodgkin's lymphoma and multiple myeloma is not required.

- Regarding non-Hodgkin's lymphoma, one of the CMS suggested to add that cyclophosphamide is used also as monotherapy dependent on disease type and stage. It was however decided to add in the heading 'cyclophosphamide may be used alone or in combination with other chemo-therapeutic agents, depending on the indication', and not specify the use of cyclophosphamide as mono or combination therapy for each indication.

Further comments from the member states regarding SmPC wording have been adequately addressed.

Instructions for reconstitution
During the procedure it was noted that there are two different innovator presentations throughout Europe: a powder for solution with mannitol as excipient (marketed in the Netherlands) and one powder for solution without any excipients. The different presentations also have different solutions for reconstitution: in the Netherlands only water for injection, in Germany saline and in Austria water for injections and/or saline.

Requested similarity studies indicate that the Dutch reference product (with mannitol) and the generic product (without mannitol) reconstituted in saline have a different osmolality: 548-549 mOsm/kg vs. 349-361 mOsm/kg. The innovator product is hyperosmotic but remains at a level (<600) which is not uncommon for parenteral products.

The MAH demonstrated that the generic product can be reconstituted in water as per Dutch reference product and demonstrated in-use stability. Furthermore, the MAH demonstrated compatibility of the reconstituted product after further dilution with ringer, saline and dextrose.
The product information was adjusted accordingly: the product can be reconstituted in water and saline and further diluted with ringer, saline and dextrose. Furthermore, the product reconstituted in saline can be directly injected. A clear instruction on reconstitution fluids is included on the label.

After finalization of the DCP for Cyclofosfamide Sandoz, the product information of the Dutch innovator Endoxan I.V. was updated for inclusion of saline as a solvent. Both innovator and generic now have similar instructions for reconstitution.

IV.4 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 Sandoz.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Myelosuppression (leukopenia, neutropenia and thrombocytopenia) • Immunosuppression • Infections, sepsis and septic shock • Nephrotoxicity, urotoxicity, hemorrhagic cystitis • Cardiotoxicity • Pulmonary toxicity • Secondary malignancies • Hepatotoxicity, Veno-occlusive liver disease (VOLD) • Sterility • Anaphylactic reactions, Cross-sensitivity with other alkylating agents • Impairment of wound healing • Nausea and Vomiting • Reduced activation of

	cyclophosphamide by interaction with other substances • Increase of the concentration of cytotoxic metabolites by interaction with other substances • Combined (increased) toxic effects by interaction with other substance • Stevens-Johnson syndrome/Toxic epidermal necrosis • Rhabdomyolysis • Hyponatremia, SIADH (syndrome of inappropriate secretion of antidiuretic hormone) • Multi-organ failure • Vascular disorders
Important potential risks	• Genotoxicity
Missing information	• None

The member states agree that routine pharmacovigilance activities are considered sufficient for this product.

IV.5 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Endoxan I.V. No new clinical studies were conducted. The product can be considered essentially similar to the reference product based on chemical-pharmaceutical properties. The indications applied for have been sufficiently justified, and risk management is adequately addressed. This medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet has not been evaluated via a user consultation study. Reference is made to another actineoplstic agent, oxaliplatin that is used in a hospital setting as well. The readability of the Oxaliplatin package leaflet (PL) was assessed and approved during procedure AT/H/0341/001/DC. Although there have been some changes in the QRD template in the meantime, this is not expected to be of great influence on the readability. For this bridging study the user-test questions were defined as key safety messages, because they reflect the central tool of determining PL readability, and they are discussed in the present bridging study. Concerning complexity of the text, user-friendly wording using layperson's language could be confirmed in the "Parent"- as well as the "Daughter" PL. In addition, both texts provide a similar structure, due to QRD template recommendations, and length, due to comparable information within their Summary of Product Characteristics (SmPCs). In addition, the applied Sandoz house-style for the package leaflet design provides clear/readable information for target patient groups as confirmed in previously performed user-tests. A comparison of design and layout elements of "Daughter" and "Parent" PL is part of the present bridging study. Overall, the bridging report is of good quality and can be accepted. Separate user testing is not required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Cyclofosfamide Sandoz 500 mg, 1000 mg and 2000 mg, powder for solution for injection/infusion have a proven chemical-pharmaceutical quality and are generic forms of Endoxan I.V. 500 mg, 1000 mg, 2000 mg powder for solution for injection. Endoxan 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 Sandoz 500 mg, 1000 mg and 2000 mg, powder for solution for injection/infusion with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 July 2014.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached