CBG MEB

Public Assessment Report

Scientific discussion

Bortezomib EBEWE 3.5 mg, powder for solution for injection

(bortezomib)

NL/H/3701/001/DC

Date: 9 May 2017

This module reflects the scientific discussion for the approval of Bortezomib EBEWE 3.5 mg, powder for solution for injection. The procedure was finalised on 6 December 2016. 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
BP	British Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EEA	European Economic Area
ERA	Environmental Risk Assessment
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
USP	United States Pharmacopoeia

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Bortezomib EBEWE 3.5 mg, powder for solution for injection from Sandoz B.V.

The indications are:

- Bortezomib EBEWE as monotherapy or in combination with PEGylated liposomal doxorubicin or dexamethasone is indicated for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation.
- Bortezomib EBEWE in combination with melphalan and prednisone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.
- Bortezomib EBEWE in combination with dexamethasone, or with dexamethasone and thalidomide, is indicated for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.
- Bortezomib EBEWE in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.

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 Velcade 3.5 mg powder for solution for injection which has been registered in the EEA by Janssen-Cilag International BV since 26 April 2004 through a centralised procedure (EU licence number EU/1/04/274).

The concerned member states (CMS) involved in this procedure were Bulgaria, Czech Republic, Estonia, Croatia, Hungary, Lithuania, Latvia, Romania, Slovenia and Slovakia.

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

II. QUALITY ASPECTS

II.1 Introduction

Bortezomib EBEWE is a white to off-white cake or powder for solution for injection

The powder is packed in 10 ml type I glass vial closed with a grey chlorobutyl rubber stopper and red flip-off aluminium seal, containing 3.5 mg bortezomib (as mannitol boronic ester).

Bortezomib Sandoz can be administered both intravenously and subcutaneously. Each vial must be reconstituted before usage with 3.5 ml (intravenous) or 1.4 ml (subcutaneous) of sodium chloride 9 mg/ml (0.9%) solution for injection. The reconstituted solution is clear with a final pH of 4 to 7.

The excipient is mannitol (E421).

II.2 Drug Substance

The active substance is bortezomib, an established active substance which is not described in the European, British Pharmacopoeia or United States Pharmacopoeia (Ph.Eur.)(BP)(USP). The active substance is very slightly soluble in water. Bortezomib is present as polymorphic form SB. The polymorphic form is routinely controlled. Bortezomib contains two asymmetric carbons. Tests for specific optical rotation and chiral purity are included in the drug substance specification.

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 of the drug substance consists of three synthetic steps to form the first intermediate and six synthetic steps to form the second intermediate. Using the two intermediates, the crude drug substance is produced in two synthetic steps. No class 1 organic solvents or metal catalysts are used. The drug substance was adequately characterised and acceptable specifications were adopted for the starting materials, solvents and reagents.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three commercial scale batches tested by the ASMF holder and three production batches tested by the MAH.

Stability of drug substance
Stability data on the drug substance were provided for three commercial scale batches stored at 25°C/60% RH (48 months) and 40°C/75% RH (six months), for two annual stability batches stored at 25°C/60% RH (36 and 24 months), and for three commercial scale batches produced after a transfer to a newly constructed production block stored at 25°C/60% RH (12 months) and 40°C/75% RH (six months). No significant changes were observed. Based on the provided stability data, the claimed re-test period of four years and storage conditions "Preserve in tight container, protected from light and store at controlled room temperature (20°C to 25°C)." are justified.

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 aim of the development was to make a drug product equivalent to the reference product Velcade. The development of the manufacturing process has been described in sufficient detail. The choice for sterilisation of the bulk solution by sterile filtration is justified. This method is also in line with the innovator product. Since the product is administered intravenously it is not necessary to prove bioequivalence. The pharmaceutical development has been adequately performed.

Manufacturing process
The manufacturing process consists of the preparation of the bulk solution, sterile filtration, filling, and lyophilisation. The manufacturing process is considered non-standard due to the aseptic processing steps. The manufacturing process was adequately described. The manufacturing process was adequately validated according to relevant European guidelines. Process validation data on the product was presented for three batches of each commercial batch size.

Control of excipients
The excipients mannitol and N_2 comply with Ph.Eur. requirements. Acceptable specifications are proposed for tert-butanol. Nitrogen and tert-butanol are excipients used in the manufacturing process, but are not present in the finished product.

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, colour of reconstituted solution, bacterial endotoxins, sterility, uniformity of dosage units, pH of the reconstituted solution, subvisible particulate contamination, tert-butanol content, related substances, assay, water, reconstitution time,

and clarity of reconstituted solution. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
The release and shelf life requirements differ with regard to the acceptance criteria for related substances. The drug product specification is acceptable. The analytical methods were adequately described and validated. Satisfactory validation data for the analytical methods have been provided. Batch analytical data three batches of each proposed commercial batch size from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product was provided for three batches of the smallest commercial batch size stored at 25°C/60% RH (36 months) and 40°C/75% RH (six months) as well as for one batch of the two larger commercial batch sizes stored at 30°C/75% RH (nine months) and 40°C/75% RH (six months). No significant changes were seen at any storage condition. Based on the photostability data, it can be concluded that the drug product is very sensitive to light. On the basis of the provided stability and forced degradation data, the claimed shelf life of 36 months and storage condition "Keep the vial in the outer carton in order to protect from light" are justified.

Stability data was provided demonstrating that the product at a concentration of 2.5 mg/ml (subcutaneous use) remains stable for seven days when stored at 20-25°C in vial/syringe and at a concentration of 1.0 mg/ml (intravenous use) remains stable for seven days at 20-25°C (room light condition) and seven days at 2-8°C.

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 Bortezomib EBEWE has 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 Bortezomib EBEWE 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 Velcade 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

Bortezomib 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

Bortezomib EBEWE 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). The quantitative composition of Bortezomib EBEWE 3.5 mg, powder for solution for injection is entirely the same as the originator. 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 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 Bortezomib EBEWE.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Peripheral motor neuropathy (including paralysis) • Autonomic neuropathy • Thrombocytopenia and Thrombocytopenia with Associated Bleeding • Neutropenia and Neutropenia with Associated Infection • Herpes zoster infection • Heart failure • Acute diffuse infiltrative pulmonary disease • Acute hypersensitivity reaction • Tumour lysis syndrome • Posterior reversible encephalopathy syndrome • Optic neuropathy and different degrees of visual impairment (up to blindness) • Hepatotoxicity • Pulmonary hypertension • Pericardial disease
Important potential risks	• Progressive multifocal leukoencephalopathy • Ventricular rhythm abnormalities • Guillain-Barré syndrome • Other central nervous system disorders • Medication/dispensing errors
Missing information	• Safety in patients with cardiac impairment or with NYHA Class III or IV impairment • Safety in patients with ECOG>2 • Second primary malignancies with BTD induction therapy

The MAH included key elements for educational material as additional risk minimisation measure regarding the potential risk for medication error with the two different routes of administration with different reconstituted concentrations.

The educational materials for healthcare professionals regarding the important potential risk of medication/dispensing errors in prescribing, dispensing, handling or administration of bortezomib, will be provided during the national phase of the procedures.

The educational materials will consist of the following:
1. Reconstitution, dosing and administration booklet
2. Reconstitution poster
3. Dosing Slide Rule
4. Induction Transplant Regimens Graph

The key elements of the educational material as proposed by the MAH are in line with that of the innovator, Velcade. The content and format of the educational material will be prepared during the national phase of the procedure.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Velcade. No new clinical studies were conducted. The MAH demonstrated essential similarity based on quality attributes. 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 bridging report making reference to Velcade. The proposed leaflet does not substantially differ from the originator's, which has been user tested. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bortezomib EBEWE 3.5 mg, powder for solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Velcade 3.5 mg powder for solution for injection. Velcade 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 Bortezomib EBEWE with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 6 December 2016.

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