Public Assessment Report

Scientific discussion

Bortezomib CF 2.5 mg/ml, solution for injection

(bortezomib)

NL/H/3938/001/DC

Date: 13 November 2018

This module reflects the scientific discussion for the approval of Bortezomib CF 2,5 mg/ml, solution for injection. The procedure was finalised on 25 January 2018. 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
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 Bortezomib CF 2.5 mg/ml, solution for injection, from Centrafarm B.V.

The indications are:

- Bortezomib CF is indicated 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 CF is indicated 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 CF is indicated 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 CF is indicated 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 hybrid 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 NV since 26 April 2004 through centralised procedure (EU/01/04/274). As the powder for solution for injection is reconstituted to 2.5 mg/ml, the reference product contains the same active substance in the same concentration as Bortezomib CF 2.5 mg/ml, solution for injection.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Germany, Denmark, Spain, Finland, France, Ireland, Italy, Luxembourg, Poland, Sweden, Slovenia and the Slovak Republic.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application, as the current product concerns a solution for injection, whereas the reference product is a powder for solution for injection.

A repeat-use procedure (NL/H/3938/001/E/001) was used to register the product in Hungary, Iceland, Norway, Portugal, Romania and the United Kingdom.

II. QUALITY ASPECTS

II.1 Introduction

Bortezomib CF is a colourless to light yellow solution with a pH-value of 4.0-5.5. Each vial contains 1.4 ml solution for injection which contains 3.5 mg bortezomib (as a mannitol boronic ester).

The solution for injection is packed in Type 1 glass 10 ml-vial with a bromobutyl stopper and an aluminium crimping cap with a coloured polypropylene flip-off cap containing 1.4 ml solution.

The excipients are: mannitol, sodium chloride and water for injections.

II.2 Drug Substance

The active substance is bortezomib, an established active substance not described in the European Pharmacopoeia (Ph.Eur.) or British Pharmacopoeia (BP). Bortezomib is a white to off-white crystalline powder, slightly hygroscopic and very slightly soluble in water. The active substance contains two chiral centres and shows polymorphism. It is fully dissolved during finished product manufacture so polymorphic form is not important for the finished product performance.

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 active substance is produced in seven convergent steps from three well defined starting materials with suitable specifications. One chiral centre originates in one of the starting materials whilst the other is introduced selectively during the process. The characterisation of the active substance and its impurities are in accordance with the European guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and includes tests for description, identity, appearance of solution, water content, chiral purity, assay, impurities, residual solvents, bacterial endotoxins, heavy metals and sulphated ash. The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Batch analytical data demonstrating compliance with this specification have been provided for 9 production scale batches.

Stability of drug substance
Stability data on the active substance have been provided for 4 batches stored in accordance ICH guidelines. No significant changes to any of the measured parameters were observed under long term or accelerated conditions. During photostability studies degradation has been observed indicating that the drug substance should be stored protected from light. The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container .

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 hybrid drug product of the reference product Velcade. Therapeutic equivalence with the reference product is based on *in-vitro* comparison. Results of the comparison of 3 batches demonstrate pharmaceutical equivalence with regard to chemical-physical parameters (i.e. appearance, clarity and degree of opalescence of liquids, degree of coloration of liquids, pH-value, extractable volume, dynamic viscosity, density, osmolality, visible particles, assay and purity profile) that could affect efficacy, including the boronic acid-ester equilibrium.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines and is a straightforward solution preparation, aseptic filtration and subsequent aseptic filling into vials process. Process validation data on the product have been presented for 3 commercial batches in accordance with the relevant European guidelines.

Control of excipients
All excipients are described in the Ph. Eur. Specifications and quality controls are according the monographs. 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, clarity and degree of opalescence of liquids, degree of coloration of liquids, pH value, extractable volume, particulate contamination (visible and sub-visible particles), identity, assay, known impurities, single unknown impurity, sum of impurities, sterility, bacterial endotoxins. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 3 industrial 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 3 batches stored at 2°C-8°C (21 months) and 25°C/60%RH (6 months). The batches were stored in the proposed packaging and according to the ICH stability guideline. Photostability studies showed that the product is sensitive to light. On basis of the data submitted, a shelf life was granted of 21 months. The storage conditions are: “store in a refrigerator at 2°C to 8°C. Keep the vial in the outer carton in order to protect form light.
The chemical and physical in-use stability after first opening and/or dilution has been demonstrated for 8 hours at 25°C when stored in the original vial and/or a polypropylene syringe. From a microbiological point of view, unless the method of opening and/or dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of user. The total storage time for the medicinal product after first opening and/or dilution should not exceed 8 hours prior to administration. During preparation for administration and during administration itself it is not necessary to protect the medicinal product from light.

Specific measures for 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 CF 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 CF is intended for hybrid 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 hybrid 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 CF 2.5 mg/ml, solution for injection 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 authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Bortezomib CF 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 CF.

- 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/dose 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 2 different routes of administration with different reconstituted concentrations.

The educational materials for healthcare professionals regarding the prescribing, dispensing, handling or administration of bortezomib, will be provided during the national phase of the procedures.

The educational material 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 is 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 hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bortezomib CF 2.5 mg/ml, solution for injection has a proven chemical-pharmaceutical quality and is a hybrid form of Velcade 1 mg and 3.5 mg, powder for solution for injection. Velcade is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of in vitro studies on the relevant quality attributes. A biowaiver has been granted.

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 CF with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 January 2018.

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
NL/H/3938/001/IB/001	Change in the shelf-life or storage conditions of the finished product; to extend the shelf-life of the finished product Bortezomib 2.5mg/ml Solution for Injection as packaged for sale from the currently approved shelf-life of 21 months to 27 months, based on extrapolation of 24 months real time stability data as per ICH recommendation/guideline.	Yes	18-04-2018	Approved	-
NL/H/3938/001/E/001	Repeat-use procedure for Hungary, Iceland, Norway, Portugal, Romania and the United Kingdom	Yes	17-09-2018	Approved	-