COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Bortezomib EVER Pharma 2.5 mg/ml, solution for injection
(bortezomib)

NL/H/5264/001/DC

Date: 17 January 2022

This module reflects the scientific discussion for the approval of Bortezomib EVER Pharma. The procedure was finalised at 14 September 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
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 EVER Pharma 2.5 mg/ml, solution for injection, from EVER Valinject GmbH.

Bortezomib EVER Pharma is indicated:

- As monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone 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.
- In combination with melphalan and prednisone for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.
- In combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.
- In combination with rituximab, cyclophosphamide, doxorubicin and prednisone 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 (original product) which has been approved throughout the EU on April 26, 2004 by Janssen-Cilag International NV. Bortezomib EVER Pharma has the same indication, strength and route of administration as the reference medicinal product Velcade but has a different therapeutic form. Therefore, a hybrid application is considered appropriate.

Similarity

The MAH has submitted an updated Module 1.7.1 addressing the potential similarity (assessment of molecular structural similarity) between Bortezomib EVER Pharma (bortezomib) and Imnovid (pomalidomide), Farydak (panobinostat), Kyprolis (carfilzomib), Darzalex (daratumumab), Ninlaro (ixazomib), Blenrep (belantamab mafodotin), Imbruvica (ibrutinib) and Tecartus (autologous anti-CD19-transduced CD3+ cells). The MAH has concluded that with regard to the similarity exercise the above mentioned products are not considered similar based on the differences in principal molecular structure. Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for these products in the treatment of multiple myeloma or mantle cell lymphoma does not prevent a marketing authorization for a generic product of Velcade.

The RMS endorses the conclusion of the MAH that with regard to the similarity exercise the above mentioned products are not considered similar based on the differences in principal molecular structure. Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for these products in the treatment of multiple myeloma or mantle cell lymphoma does not prevent a marketing authorization for a generic product of Velcade.

The concerned member states (CMS) involved in this procedure were Belgium, Denmark, Spain, Finland, France, Hungary, Ireland, Italy, Norway, Portugal and Sweden.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Bortezomib EVER Pharma is a clear, colourless to light yellow solution with a pH of 4.0 – 5.5.

1 ml solution for injection contains 2.5 mg bortezomib (as a mannitol boronic ester).

Each vial with 1 ml solution for injection contains 2.5 mg bortezomib (as a mannitol boronic ester). Each vial with 1.4 ml solution for injection contains 3.5 mg bortezomib (as a mannitol boronic ester). Each vial contains an additional overfill of 0.2 ml.

For subcutaneous injection no dilution is necessary.
1 ml of solution for subcutaneous injection contains 2.5 mg bortezomib.

For intravenous injection dilution is necessary.
After dilution 1 ml of solution for intravenous injection contains 1 mg bortezomib.

The solution is packed in a colourless glass vial (type I) with a fluoropolymer-coated bromobutyl rubber stopper and an aluminium cap with plastic flip-off.

The excipients are: mannitol, sodium chloride, sodium hydroxide (for pH-adjustment), hydrochloric acid (for pH-adjustment) 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.). The active substance is a white to off-white solid or powder, consistently manufactured as polymorphic Form I (as trimeric boroxine) and is very

slightly soluble in water. Polymorphic form is not a critical attribute of the drug substance as the related finished product is a solution. In aqueous solution the trimeric form (boroxine) of bortezomib undergoes hydrolysis to its monomeric boronic acid form. Bortezomib incorporates two stereogenic centres and is supplied as the (R,S) enantiomer. The stereochemistry of the active substance is controlled and was shown not to change during manufacture and storage of the drug product.

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 synthesis of bortezomib is described in six synthetic steps followed by a final purification step. No class 1 organic solvents or heavy metal catalysts are used in the process. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance

The active substance specification has been established in-house by the MAH and is largely in line with the specification from the active substance manufacturer, with additional requirements for impurities. 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 batches.

Stability of drug substance

Stability data on the active substance have been provided for three production scaled batches stored at -20°C (up to 36 months) and 5°C (up to six months) in accordance with applicable European guidelines demonstrating the stability of the active substance for 24 months. The batches were evaluated for appearance, identity, purity and related substances, water, assay, microbial purity and bacterial endotoxins. Except for an increase in impurities (within the specification), no clear trends or changes were observed. Results of a photostability study in accordance with ICH Q1B showed that the active substance is light sensitive. Based on stability data presented the proposed retest period of 24 months with storage conditions 'Store in a freezer under the temperature -20 ± 5 °C in the original packaging protected from light and moisture' is considered acceptable.

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 performed were the characterisation of the reference product and performance of studies investigating the sensitivity of the product to headspace oxygen, pH and light. The stability of the product was shown not impacted within a pH range of 4.0-5.5 and the product was shown to be light sensitive. The choice of the packaging has been justified. No bioequivalence studies have been performed in support of this application, but this is acceptable. Therapeutic equivalence has been sufficiently demonstrated based on comparative in vitro data versus the reference product. The choice of the sterilisation method is justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The main steps of the process are the compounding of the bulk solution, pre-filtration, sterile filtration and filling of vials. The sterilisation cycles for the primary packaging components (glass vials and rubber stoppers) are adequate. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scaled batches.

Control of excipients

The excipients comply with 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, clarity and opalescence of solution, colour of solution, visible particles, particulate matter: sub-visible particles, pH, extractable volume, identification, assay, related substances, bacterial endotoxins and sterility. Except for related substances, the release and shelf-life requirements are identical. The specification is acceptable. An adequate nitrosamine risk evaluation has been provided, justifying the absence of further controls. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full scaled batches of each presentation, demonstrating compliance with the release specification. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Stability of drug product

Stability data on the product have been provided for three production scaled batches of each presentation stored at 2-8°C (18 months) and 25°C/60% RH (six months) in accordance with applicable European guidelines demonstrating the stability of the product for one year. The batches were stored in a colourless glass vial (type I) with a rubber stopper and an aluminium cap with plastic flip-off. At accelerated storage conditions a significant increase in impurities is already seen after three months storage. The long-term results seem to show a decrease in assay (results are variable) and increase in impurities. Photostability studies were performed in accordance with ICH recommendations and showed that the product is not stable when

exposed to light. Freeze-thaw cycling studies have been performed, showing no negative impact on the drug product quality. On basis of the data submitted, a shelf life was granted of one year. The labelled storage conditions are: 'Store in a refrigerator (2-8°C)' and 'Keep the vial in the outer carton in order to protect from light'.

Stability data has been provided demonstrating that the product remains stable for 28 days at 2-8°C protected from light, 28 days at 25°C protected from light or 24 hours at 25°C in normal indoor lighting conditions when stored in the original vial and/or a polypropylene syringe after first opening and/or dilution.

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 EVER Pharma 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 EVER Pharma 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 EVER Pharma 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.

Bortezomib EVER Pharma 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 authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Bortezomib EVER Pharma 2.5 mg/ml 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 product is to be administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference product and the excipients are not expected to affect the pharmacokinetics of the active substance of the prepared solution for infusion. Therefore, a bioequivalence study is not needed. The current product can be used instead of its reference product.

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 Bortezomib EVER Pharma.

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 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 Velcade. 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

The package leaflet (PL) 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 language used for the purpose of user testing the PL was English. The test consisted of: a pilot test with two participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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 EVER Pharma 2.5 mg/ml, solution for injection has a proven chemical-pharmaceutical quality and is a hybrid form of Velcade. 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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Bortezomib EVER Pharma with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 September 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