COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Bortezomib Genthon 2.5 mg powder for solution for injection

(bortezomib)

NL/H/3174/003/DC

Date: 25 September 2019

This module reflects the scientific discussion for the approval of Bortezomib Genthon 2.5 mg powder for solution for injection. The procedure was finalised at 20 June 2019. 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
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 Genthon 2.5 mg powder for solution for injection from Genthon B.V.

The indications are:

- Bortezomib Genthon 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 Genthon 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 Genthon 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 Genthon 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 1 mg/ml or 2.5 mg/ml depending on the route of administration, the reference product contains the same active substance in the same concentration as Bortezomib Genthon 2.5 mg powder for solution for injection.

The concerned member states (CMS) involved in this procedure were Germany, France, Italy, and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

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

The powder is packed in a colourless type I glass 10R (nominal volume 10 ml) vial with a bromobutyl rubber stopper and a yellow flip-off cap. Each vial contains as active substance 2.5 mg of bortezomib (as a mannitol boronic ester).

The excipient is mannitol (E421).

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 insoluble in water. Bortezomib shows polymorphism. The active substance has two chiral centres and is manufactured as the RS-enantiomer. The drug substance is manufactured and supplied in its anhydride form as a trimer.

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. No class 1 organic solvents or heavy metal catalysts are used in the process. Acceptable specifications have been adopted for the starting materials, solvents and reagents used in the process.

Quality control of drug substance

The drug substance specification applied by the MAH is the same as that applied by the ASMF holder. The drug substance specification is acceptable. Batch analytical data demonstrating compliance with the specification have been provided on four full-scale batches of drug substance.

Stability of drug substance

Stability data on the active substance have been provided for three full-scale batches that were stored in a freezer at -20°C (24 months). One batch was stored in a refrigerator at 2-8°C (six months). The batches stored in a freezer showed an increase in one of the impurities and

no changes in any of the other tested parameters. When stored in a refrigerator, out-of-specification results were reported for assay and impurities after six months storage. Bortezomib was stable for one month in a refrigerator. The proposed retest period of 24 months when stored under an inert atmosphere in its original packaging at -20°C in a dry and dark place is 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 development of the product has been focused on the additional 2.5 mg strength of the generic drug product Bortezomib powder for solution for injection. The formulation development, packaging selection, optimization of the current lyophilisation process of the 3.5 mg strength to apply to the 2.5 mg strength and determination of the critical temperatures for the 2.5 mg lyophilisation process have been sufficiently examined and discussed.
Sufficient information has been provided on the pharmaceutical development of 2.5 mg strength taking into account the already approved data for Bortezomib Genthon 1 mg and 3.5 mg powder for solution for injection.

Manufacturing process

The main steps of the manufacturing process are the dissolution of the drug substance and mannitol in a mixture of water for injections and tert-butanol (which are removed during processing), sterilisation of the bulk solution by sterile filtration followed by aseptic filling and lyophilisation. The details of the lyophilisation cycle, the description of the methods and conditions of sterilisation of the primary packaging materials and maximum holding time for the bulk solution are sufficiently provided.
The manufacturing process is considered a non-standard process given the lyophilisation step combined with sterile filtration. A limited process validation has been performed for the 2.5 mg strength on the proposed production batch size. This is considered acceptable as the 2.5 mg strength is proportional in formulation to the already approved 1 mg and 3.5 mg strengths. It is filled in the same vial and it is manufactured using the same equipment and lyophilisation process as the 3.5 mg strength. The preparation of the 1 mg/ml bulk solution is the same for all the involved strengths.

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 appearance, reconstitution time, pH of the reconstituted solution, colour and clarity of the reconstituted solution, uniformity of dosage units, water content, residual tert-butanol, particulate matter, identity, assay, impurities, sterility and bacterial endotoxins. Except for related substances, the release and shelf-life

requirements are identical. 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 sufficient 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. Three full scaled batches of 2.5 mg strength were stored at 25°C/60% RH (18 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. All parameters remain within the specified limits. The proposed shelf life of 36 months is considered acceptable in light of the available stability study data for the 2.5 mg strength and the data for the already approved strengths (1 mg and 3.5 mg) of the drug product. The approved storage conditions are: "*Keep the vial in the outer carton in order to protect from light. This medicinal product does not require any special temperature storage conditions.*"
The claimed in-use shelf life for the reconstituted solution (eight hours storage at 25°C/60% RH in the dark) is also acceptable.

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 Genthon 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 Genthon 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 Genthon 2.5 mg powder for solution for injection is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "APPENDIX II 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 and in case of subcutaneous route when the test product is of the same type of solution (aqueous) and contains the same concentration of the same active substance and the same excipients in similar amounts as the medicinal product currently approved (NfG CPMP/EWP/QWP/1401/98 Rev. 1/ Corr). The quantitative composition of Bortezomib Genthon 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 Genthon.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Acute diffuse infiltrative pulmonary disease • Acute hypersensitivity reaction • Autonomic neuropathy • Cardiac failure • Hepatotoxicity • Herpes zoster infection • Neutropenia and neutropenia with associated infection • Optic neuropathy and different degrees of visual impairment (up to blindness) • Pericardial disease • Peripheral motor neuropathy (including paralysis) • Posterior reversible encephalopathy syndrome • Pulmonary hypertension • Thrombocytopenia and thrombocytopenia with associated bleeding • Tumour lysis syndrome
Important potential risks	• Guillain-Barré Syndrome • Medication/Dispensing errors • Other central nervous system disorders • Progressive multifocal leukoencephalopathy • Ventricular rhythm abnormalities
Missing information	• Second primary malignancies with dexamethasone and thalidomide induction therapy • Use in patients with heart disease • Use in patients with Eastern Cooperative Oncology Group (ECOG)>2

In line with the reference product, additional risk minimisation measures (educational material) regarding the safety concern “medication/dispensing errors” are proposed.

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.

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the other risks and areas of missing information.

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 3.5 powder for solution for injection. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

In addition, the MAH has previously performed a successful user test of an Eplerenone 25 mg and 50 mg film-coated tablets PL. This user test is used to support the changes made to the proposed PL compared to the parent PL (e.g. house style).

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bortezomib Genthon 2.5 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.

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 Genthon with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 June 2019.

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