COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Bortezomib Synthon 2.5 mg, powder for solution for injection

(bortezomib)

NL/H/3173/002/DC

Date: 20 March 2019

This module reflects the scientific discussion for the approval of Bortezomib Synthon 2.5 mg, powder for solution for injection. The procedure was finalised on 5 September 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
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
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 Synthon 2.5 mg, powder for solution for injection from Synthon B.V.

The indications are:

- Bortezomib 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 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 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 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 line extension application for the authorisation of the new strength (2.5 mg) to the previously approved Bortezomib Synthon 3.5 mg powder for solution for injection.

The application refers to reference product Velcade 3.5 mg powder for solution for injection, by Janssen-Cilag International NV, registered in The Belgium since 28 February 20 September 2012. The innovator Velcade does not have a 2.5 mg strength.

The application is submitted in accordance with Article 10(3) of Directive 2001/83/EC as amended (hybrid application) as it concerns a new strength.

The concerned member states (CMS) involved in this procedure were Finland, Iceland and Sweden

II. QUALITY ASPECTS

II.1 Introduction

Bortezomib Synthon 2.5 mg is a white to off-white cake or powder. Each vial contains 2.5 mg bortezomib (as a mannitol boronic ester).

Bortezomib 2.5 mg can be administered both intravenously and subcutaneously.

The powder is supplied in colourless type I glass vials (10 ml) with a bromobutyl rubber stopper and a yellow flip-off cap.

Mannitol (E421) is present as an excipient.

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). 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

(6 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 6 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 development of the product has been described, the choice of excipients is justified and their functions explained. The aim of the development has been focused on the additional strength of the drug product Bortezomib 3.5 mg powder for solution for injection, i.e. a 2.5 mg strength. The formulation development, packaging selection, optimisation 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.
Furthermore, sufficient information has been provided on the pharmaceutical development of 2.5 mg strength talking into account the already approved data for Bortezomib 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.
Details specific for the 2.5 mg strength have been provided. This section contains additional information as compared for the 1 mg and 3.5 mg strengths, namely 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 laid down. 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

Information on excipients has not been submitted. It is considered acceptable as excipients have not changed as compared to the existing/approved strengths. The excipients comply with Ph.Eur. requirements. These specifications are acceptable.

Quality control of drug product

The drug product specification, analytical test methods and their validations are in line with the specifications for the existing/approved strengths.

The product 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. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three pilot-scale batches of 2.5 mg, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product have been provided; three full-scale batches of 2.5 mg were stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in type I glass vials with rubber stopper and flip-off cap. At both storage conditions an increase in impurities is seen. No other trends or changes are observed. All parameters remain within the specified limits. The product was shown to be sensitive to light. The claimed 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 proposed shelf-life of 3 years and storage conditions 'This medicinal product does not require any special temperature storage conditions' and 'Keep the vial in the outer carton in order to protect from light' are justified.

Stability data has been provided demonstrating that the product remains stable for 8 hours at 25°C/60% RH in the dark both in a vial and in a polypropylene syringe.

Specific measures concerning the prevention of the transmission of animal spongiform encephalo-pathies

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 Synthon 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 Synthon 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

Pharmacodynamic, pharmacokinetic and toxicological properties of bortezomib are well known. Bortezomib is a widely used, well-known active substance. 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 Synthon 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 solution containing the same active substance in the same concentration as the currently authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The 2.5 mg strength formulation contains the same active substance in the same concentration (concentration after reconstitution is 1 mg/ml or 2.5 mg/ml, depending on the route of administration, and it is identical as in the innovator products) and the same excipients in similar amounts as the reference product Velcade. 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 Synthon.

Summary of safety concerns	
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

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 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 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 reference product. 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 (PL) has not been evaluated via a user consultation study. A bridging report has been submitted. A comparison between the current PL of Velcade 3.5 mg powder for solution for injection and the proposed PL of Bortezomib has been made. The proposed leaflet does not substantially differ from the originator's, which has been user tested. The house style of the MAH has been successfully tested in previous procedures. Therefore, the member states agree that bridging is justified.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bortezomib Synthon 2.5 mg, powder for solution for injection has a proven chemical-pharmaceutical quality and is a line extension form of Bortezomib 3.5 mg powder for solution for injection and a hybrid 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, have granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 September 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