19 September 2019
EMA/CHMP/552819/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bortezomib Fresenius Kabi

International non-proprietary name: bortezomib

Procedure No. EMEA/H/C/005074/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Bortezomib Fresenius Kabi
Applicant:	Fresenius Kabi Deutschland GmbH Else-Kroner Strasse 1 61352 Bad Homburg v.d.Hohe GERMANY
Active substance:	BORTEZOMIB
International non-proprietary name/Common name:	bortezomib
Pharmaco-therapeutic group (ATC Code):	antineoplastic agents, other antineoplastic agents (L01XX32)
Therapeutic indication(s):	Bortezomib 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.
Pharmaceutical form(s):	Powder for solution for injection
Strength(s):	3.5 mg
Route(s) of administration:	Intravenous use, Subcutaneous use
Packaging:	vial (glass)
Package size(s):	1 vial

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List of abbreviations

ASMF	Active Substance Master File
CPP	Critical process parameter
CQA	Critical Quality Attribute
DSC	Differential Scanning Calorimetry
EC	European Commission
EU	European Union
GC	Gas Chromatography
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared
LDPE	Low density polyethylene
LoQ	Limit of Quantitation
NMR	Nuclear Magnetic Resonance
PDE	Permitted Daily Exposure
Ph. Eur.	European Pharmacopoeia
QbD	Quality by design
QTPP	Quality target product profile
RH	Relative Humidity
SmPC	Summary of Product Characteristics
USP	United States Pharmacopoeia
UV	Ultraviolet
XRPD	X-Ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Fresenius Kabi Deutschland GmbH submitted on 17 September 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Bortezomib Fresenius Kabi, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 31 May 2018.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in the Union the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

- Bortezomib 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.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and literature references instead of non-clinical and clinical data unless justified otherwise.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Velcade, 3.5 mg powder for solution for injection
- Marketing authorisation holder: Janssen Cilag International NV
- Date of authorisation: 26-04-2004
- Marketing authorisation granted by: Community
- Community Marketing authorisation number: EU/1/04/274/001

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Velcade, 3.5 mg powder for solution for injection
- Marketing authorisation holder: Janssen Cilag International NV
- Date of authorisation: 26-04-2004
- Marketing authorisation granted by: Community
- Community Marketing authorisation number: EU/1/04/274/001

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The applicant did not seek Scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: Kolbeinn Gudmundsson

The application was received by the EMA on	17 September 2018
The procedure started on	4 October 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	19 December 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	7 January 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	31 January 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	26 April 2019
The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	3 June 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	6 June 2019

The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	27 June 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	8 August 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	30 August 2019
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	10 September 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Bortezomib Fresenius Kabi on	19 September 2019

2. Scientific discussion

2.1. Introduction

This application is for marketing authorization of Bortezomib Fresenius Kabi 3.5 mg Powder for Solution for Injectionis based on Directive 2001/83/EC Article 10 (1): a generic application, referring to the reference product Velcade 3.5 mg Powder for Solution for Injection of the Marketing Authorisation Holder, Janssen-Cilaq International NV, Belgium which has been authorized in accordance with Union provisions in force for not less than 10 years in the EEA. Velcade 3.5 mg Powder for Solution for Injection was first authorised within the EU on the 26-04-2004 under registration number EU/1/04/274/001.

Bortezomib is a selective, reversible inhibitor of 26S proteasome in mammalian cells, a large protein complex that degrades ubiquinated proteins. Inhibition of the 26S proteasome prevents targeted proteolysis and affects multiple signalling cascades within the cell, ultimately resulting in cancer cell death. At 10 µM concentrations, bortezomib does not inhibit any of a wide variety of receptors and proteases screened and is more than 1,500 fold more selective for the proteasome than for its next preferable enzyme. The kinetics of proteasome inhibition were evaluated in vitro, and bortezomib was shown to dissociate from the proteasome with a t½ of 20 minutes, thus demonstrating that proteasome inhibition by bortezomib is reversible.

Bortezomib mediated proteasome inhibition affects cancer cells in a number of ways, including, but not limited to, altering regulatory proteins, which control cell cycle progression and nuclear factor kappa B (NF kB) activation. Inhibition of the proteasome results in cell cycle arrest and apoptosis. NF kB is a transcription factor whose activation is required for many aspects of tumourigenesis, including cell growth and survival, angiogenesis, cell-cell interactions, and metastasis. In myeloma, bortezomib affects the ability of myeloma cells to interact with the bone marrow microenvironment.

The reference product Velcade is indicated as a monotherapy or in combination with other anticancer products in treatment of multiple myeloma for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation. The currently approved indication for Bortezomib is as follows:

Velcade 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.

Velcade 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.

Velcade 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.

Velcade 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.

Bortezomib Fresenius Kabi 3.5 mg powder for solution for injection can be used for either intravenous or subcutaneous administration, but reconstitution is different. This corresponds to the mode of administration of the reference medicinal product (Velcade 3.5 mg powder for solution for injection, Janssen-Cilag International NV, Belgium).

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a powder for solution for injection containing 3.5 mg per vial of bortezomib (as mannitol boronic ester).

The only other ingredient is mannitol (E421).

The product is available in clear type I glass vial with grey chlorobutyl rubber stoppers and blue aluminium flip-off overseals as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The information on bortezomib was provided in the form of an active substance master file (ASMF).

The chemical name of bortezomib is [(1*R*)-3-methyl-1-[[(2*S*)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)-amino]propyl]amino]butyl]boronic acid corresponding to the molecular formula $C_{19}H_{25}BN_4O_4$. It has a relative molecular mass of 384.24 g/mol and the following structure:

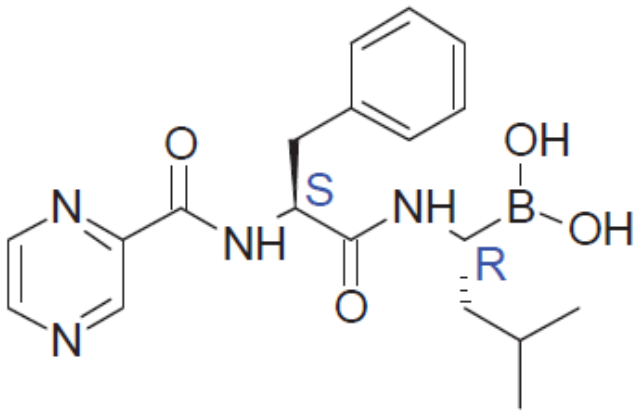

Figure 1: active substance structure

The chemical structure of bortezomib was elucidated by a combination of ^{1}H, ^{13}C and ^{11}B NMR spectroscopy, elemental analysis, high resolution mass spectrometry, infrared spectroscopy, and specific optical rotation. The solid state properties of the active substance were measured by differential scanning calorimetry (DSC) and x-ray powder diffraction (XRPD). Based on the data in the original submission, there was uncertainty as to the nature of the active substance, which could be present as the free boronic acid, or as the trimeric boroxine, and which have different molecular weights. This resulted in two major objections. The first related to the characterization data itself. The second related to doubts about the actual bortezomib content of the finished product, given the difference in molecular weights of the monomeric and trimeric forms, and the potential impact on product strength (5% difference in assay between the two). In response, the applicant provided further NMR and XRPD data confirming that the active substance is isolated as a monomeric boronic acid rather than as a dimer or trimeric boroxine. This also resolved the uncertainty about the actual bortezomib content of the active substance.

Although bortezomib is known to exhibit polymorphism based on literature data, the polymeric form produced by the proposed manufacturer is consistent. Nonetheless, this is not considered important as the active substance is dissolved and reacts with mannitol to form a boronic ester during finished product manufacture.

The active substance is a slightly hygroscopic, white to off-white crystalline powder. Bortezomib is practically insoluble in aqueous media, irrespective of pH, but freely soluble in methanol. Addition of ^{t}BuOH increases solubility in water.

Bortezomib contains two chiral centres and enantiomeric purity is controlled routinely by specific optical rotation.

Manufacture, characterisation and process controls

Detailed information on the manufacturing process of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Bortezomib is synthesized in 7 chemical transformation steps and 2 recrystallisations using well-defined starting materials with acceptable specifications. The first 4 steps are carried out by 1 manufacturer and the final 3 steps are carried out by a second manufacturer. All 3 potential stereoisomers are controlled in the active substance specification by a chiral HPLC method.

Adequate in-process controls are applied during the synthesis and these are documented in the restricted part of the ASMF. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. One possible genotoxic impurity, both a precursor to one of the starting materials and a reagent used in the process, has been demonstrated to be completely purged below detectable levels. Therefore, no control of this impurity is deemed necessary in any intermediate or the active substance.

The active substance is packaged in triple LDPE bags stored inside two heat-sealed triple-laminated aluminium pouches, all flushed with nitrogen prior to sealing. These are further stored within HDPE drums. The LDPE bags comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for description, solubility (in-house), identity (IR, HPLC), appearance of solution (Ph. Eur.), water content (coulometry), specific optical rotation (in-house),

residual solvents (GC), related substances (HPLC), stereoisomers (chiral HPLC), assay (HPLC), bacterial endotoxins (Ph. Eur.) and microbial enumeration (Ph. Eur.) and absence of *E. coli* (in-house).

Impurities limits are set in line with ICH Q3A. The limit for total impurities is considered acceptable based on batch analysis data.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 3 pilot scale of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 pilot scale batches of active substance from the proposed manufacturers stored in the intended commercial package for up to 18 months under long term conditions (5±3 ºC) and for up to 6 months under accelerated conditions (25 ºC / 60% RH) according to the ICH guidelines were provided. Parameters investigated include description, identification, appearance of solution, water content, related substances, stereoisomers, assay, specific optical rotation, bacterial endotoxins and microbial enumeration. No significant changes were observed for any of the measured parameters, other than a small fluctuation (without trend) in the water content. All parameters remained within specification.

Photostability testing was conducted on the finished product and is discussed the section on pharmaceutical development and stability of the finished product. In addition, stability under stressed conditions was evaluated in support of analytical method validation. Significant degradation occurs under photolytic, basic and oxidative conditions. Degradation also occurs to a lesser extent under acidic conditions. No degradation was observed under thermal stress.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 24 months refrigerated (5±3 ºC) in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is a white to off-white powder or cake containing bortezomib as active substance and comes in clear type I glass vials with grey chlorobutyl rubber stoppers. It is reconstituted with 0.9% w/v sodium chloride solution for injection, although the diluent is not provided. The reconstituted finished product is clear, colourless solution.

The purpose of the pharmaceutical development was to develop a generic formulation of Bortezomib 3.5 mg/vial Powder for Solution for Injection which is equivalent to the reference product, Velcade. The proposed formulation has the same pharmaceutical form, qualitative and quantitative composition as the reference product.

Bortezomib is practically insoluble in aqueous media but can be dissolved in water with the addition of an alcoholic co-solvent. Different polymorphic forms are known, although these are not relevant as the active substance is dissolved during finished product manufacture. The active substance is photosensitive.

As for the reference product, mannitol is the only excipient used, as a bulking agent, and forms a boronic ester with bortezomib during formulation. NMR data was submitted to demonstrate that the test and

reference product formulations contain equivalent amounts of boronic aster and free boronic acid. Mannitol is a well-known pharmaceutical ingredient and its quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

No bioequivalence study was required since the finished product is a parenteral dosage form and is administered as an aqueous solution containing the same active substance in the same concentration as the reference product.

Some aspects of quality by design (QbD) were applied to develop a generic finished product that is pharmaceutically and therapeutically equivalent to the reference medicinal product. The quality target product profile (QTPP) was defined on the basis of reference product label, characterization of reference product and pharmacopoeial and parenteral requirements.

The critical quality attributes (CQAs) were identified based on the QTPP. A risk assessment was conducted to evaluate the impact of active substance and excipient attributes, process parameters, process equipment and packaging components on these CQAs and the outcome was used to guide further investigations. Development studies were performed on those factors considered most likely to impact the finished product CQAs. The manufacturing process development studies were performed together with the formulation development. The proposed materials of the formulation vessels, filters, and tubing are compatible with the finished product and do not result in untoward extractables and leachables. Terminal sterilization is not possible, given the lyophilized formulation, so sterile filtration and subsequent aseptic processing is required. Drawing on these conclusions, the processes for preparation of bulk solution and sterile filtration were optimised to minimise degradation and ensure a sterile product and that a readily soluble cake is formed.

The primary packaging is clear type I glass vials with grey chlorobutyl rubber stoppers and blue aluminium flip-off overseals. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: compounding, sterile filtration, lyophilization, and packaging. The process is considered to be a non-standard manufacturing process.

The manufacturing process has been validated on 3 consecutive production scale batches of finished product. Holding time, filter validation, container closure integrity and media fill studies were conducted as part of the validation. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls applied during compounding, filtration, filling and following lyophilization are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including description, identity (UV, HPLC), water content (Ph. Eur.), uniformity of dosage units (Ph. Eur.), reconstituted solution properties (time, appearance, colour, pH, clarity and particulate matter (Ph. Eur.)), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.), related substances (HPLC), assay (HPLC), residual solvents (GC) and seal integrity (in-house).

Limits for impurities and residual solvents have been adequately justified. Assessment of elemental impurities was performed during the pharmaceutical development according the ICH Q3D, considering the active substance manufacturing process, raw materials, equipment and container closure system and the risk of their presence was considered to be low. Furthermore, 3 batches of finished product were

tested for relevant elemental impurities demonstrating that none are detected above the limit of quantitation (LoQ) which was below 30% of the PDE for each element. The information on the control of elemental impurities is satisfactory.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results were provided for 3 production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 production scale batches of finished product stored for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for description, water content, reconstituted solution properties, related substances and assay. Seal integrity was tested instead of sterility and bacterial endotoxins. The analytical procedures used are stability indicating. There were no significant trends to most parameters under either long term or accelerated conditions. There was a slight increase in two impurities (and total impurities), more so at higher temperature/humidity, but the increase was well within the specification limits. The product is considered to be physically, chemically, and microbiologically stable.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is photosensitive and degradation is observed in the primary packaging. However, the secondary carton was shown to provide sufficient protection from light.

A thermal cycling study was performed on 1 batch at 2-8 °C for two days, followed by 40°C/75% RH for two days, and at -20 °C for two days, followed by 40 °C/75% RH for two days. A thermal excursion study was performed on 1 batch for two weeks at -20 °C, 2-8 °C and at 60 °C. The stability of the finished product was found to be well within the defined limits during both studies.

A reconstitution stability study was conducted on 3 batches of finished product. These were reconstituted with either 3.5 ml (for intravenous use) or 1.4 ml (for subcutaneous use) of sterile 0.9% sodium chloride solution for injection to give a solution containing either 1 mg/ml or 2.5 mg/ml of bortezomib, respectively. The study was conducted in vials as well as in syringes at 25 °C/60% RH for 96 hours and at 2-8 ºC for 8 days. The reconstituted solutions were found to be stable both in the vials and syringes. Since the finished product contains no preservative, aseptic technique is mandated during preparation of the reconstituted solutions.

Based on available stability data, the proposed shelf-life of 24 months without special storage conditions as stated in the SmPC (section 6.3) is acceptable.

The chemical and physical in-use stability of the reconstituted solution has been demonstrated at concentrations of 1 mg/ml and 2.5 mg/ml for 96 hours at 25 °C and 8 days at 2-8°C, when stored in the original vial and/or a syringe.

From a microbiological point of view, the reconstituted solution should be used immediately after preparation. If not used immediately, in-use storage times and conditions prior to use are the

responsibility of the user. The total storage time for the reconstituted medicinal product should not exceed 96 hours (if stored at 25 °C) and 8 days (if stored at 2-8 °C) prior to administration.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The major objections on the lack of active substance clarification data, uncertainty about the nature of the isolated active substance, and the consequent potential impact on bortezomib content of the finished product were convincingly resolved during the procedure. Clear instructions for preparation and handling of the reconstituted solutions have been included in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Bortezomib Fresenius Kabi manufactured by Fresenius Kabi Deutschland GmbH is considered unlikely to result in any significant increase in the combined sales volumes for all bortezomib containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.3. Discussion on non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the CHMP agreed that no further non-clinical studies are required.

The impurity profile of applicant's bortezomib is comparable to that of Velcade. Thus, additional toxicology studies to qualify the impurity profile of the drug product are not required.

In line with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), the justification for not providing new ERA studies is acceptable.

2.3.4. Conclusion on the non-clinical aspects

The CHMP is of the opinion that the applicant has justified the absence of non-clinical studies based on the literature review and the claim that Bortezomib Fresenius Kabi is a generic of the reference product Velcade. The literature data presented in the dossier is considered acceptable and sufficient for the assessment of non-clinical aspects of Bortezomib Fresenius Kabi in the applied indications.

2.4. Clinical aspects

2.4.1. Introduction

The clinical overview on the clinical pharmacology, efficacy and safety has been provided. The Clinical sections of the SmPC of Bortezomib Fresenius Kabi are in accordance with the reference product Velcade 3.5 mg powder for solution for injection, Janssen-Cilag International NV, a Centralized product EMEA/H/C/000539, the date of authorisation is 2004-04-26.

Relevant for the assessment are the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product. The CHMP considers that the clinical overview on the clinical pharmacology, efficacy and safety is adequate.

Exemption

No bioequivalence study was submitted to support the application. According to Appendix II to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. This is the case here. Both products, generic product Bortezomib Fresenius Kabi and the reference product Velcade, contain 3.5 mg of the same active substance, bortezomib (as mannitol boronic ester), and the same excipients (mannitol E421 and nitrogen). Therefore, it is concluded that there is no difference between the Bortezomib Fresenius Kabi and Velcade. A bioequivalence study is not required.

2.4.2. Pharmacokinetics

No new pharmacokinetic studies were presented and no such studies are required for this application.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

The clinical overview on the clinical pharmacology, efficacy and safety has been provided and is adequate.

No bioequivalence study was submitted to support the application, this is in accordance with the Appendix II to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

Bortezomib Fresenius Kabi is considered essentially similar to Velcade, Janssen-Cilag International NV.

2.4.6. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Bortezomib Fresenius Kabi and justifications that the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

2.5. Risk management plan

Summary of safety concerns

The applicant identifies the following safety concerns in the RMP:

Table 1: Summary of safety concerns:

Summary of safety concerns	
Important identified risks	– Heart failure – Hepatotoxicity – Acute hypersensitivity reactions – Tumour lysis syndrome – Peripheral motor neuropathy (including paralysis) – Autonomic neuropathy – Acute diffuse infiltrative pulmonary disease – Pericardial disease – Pulmonary hypertension – Herpes zoster infection – Posterior reversible encephalopathy syndrome (PRES) – Optic neuropathy and different degrees of visual impairment (up to blindness) –Thrombocytopenia and and thrombocytopenia with associated bleeding – Neutropenia and neutropenia with associated infection
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 VcTD induction therapy

Pharmacovigilance plan

The applicant has submitted on 08 August 2019 an updated version of the RMP (ver.1.2 data) as part of the responses to the 180 LoOI.

No additional pharmacovigilance activities are planned by the applicant.

In line with originator, the applicant updated the relevant sections of RMP with further activities still considered to be routine in line of the reference medical product, in particular the applicant implemented the following Routine pharmacovigilance activities:

- Progressive Multifocal Leukoencephalopathy: a questionnaire to gather more information on the individual Progressive Multifocal Leukoencephalopathy (PML) cases and close monitoring at regular intervals for any new or worsening neurological symptoms or signs suggestive of PML in patient treated with Bortezomib) for early detection and management of PML to evaluate case reports with relevant neurological findings, which could be indicative of PML.

- Second primary malignancies with BzTD induction therapy: to characterize case reports of second primary malignancies when bortezomib is given in combination with thalidomide.

- Medication/dispensing errors: Ongoing monitoring with routine pharmacovigilance activities including a targeted follow-up questionnaire

- Optic neuropathy: Ongoing monitoring with routine pharmacovigilance activities including a targeted follow-up questionnaire For Patients Who Develop Visual Problems

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Heart failure	Guidance in SmPC section 4.4 "Special warnings and precautions for use" and section 4.8 "Undesirable effects" Guidance in PL Section 2, What you need to know before you use	- Single AE report analysis, - Signal detection, Aggregate Reports - Review in PSURs

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Bortezomib Fresenius Kabi and section 4 "Possible side effects"	
Hepatotoxicity	Guidance in SmPC section 4.4 "Special warnings and precautions for use" and section 4.8 "Undesirable effects" Guidance in PL section 2 "What you need to know before you use Bortezomib Fresenius Kabi" and section 4 "Possible side effects"	- Single AE report analysis, - Signal detection, Aggregate Reports - Review in PSURs
Acute hypersensitivity reactions	Guidance in SmPC section 4.3 "Contraindications", and section 4.8 "Undesirable effects" Guidance in PL section 2 "What you need to know before use Bortezomib Fresenius Kabi "and section 4 "Possible side effects".	- Single AE report analysis, - Signal detection, Aggregate Reports - Review in PSURs
Tumour lysis syndrome	Guidance in SmPC section 4.4 "Special warnings and precautions for use" and section 4.8 "Undesirable effects" Guidance in PL section 2 "What you need to know before you use Bortezomib Fresenius Kabi" and section 4 "Possible side effects"	- Single AE report analysis, - Signal detection, Aggregate Reports - Review in PSURs
Peripheral motor neuropathy (including paralysis)	Guidance in SmPC section 4.2 "Posology and method of administration", section 4.4 "Special warnings and precautions for use" and section 4.8 "Undesirable effects" Guidance in PL Section 2, What you need to know before you use Bortezomib Fresenius Kabi and section 4 "Possible side effects"	- Single AE report analysis, - Signal detection, Aggregate Reports - Review in PSURs
Autonomic neuropathy	Guidance in SmPC section 4.4 "Special warnings and precautions for use" Listed in SmPC section 4.8 "Undesirable effects" Guidance in PL Section 2, What you need to know before you use	- Single AE report analysis, - Signal detection, Aggregate Reports - Review in PSURs

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Bortezomib Fresenius Kabi and section 4 "Possible side effects"	
Acute diffuse infiltrative pulmonary disease	Guidance in SmPC section 4.3 "Contraindications", 4.4 "Special warnings and precautions for use", Listed in SmPC section 4.8 "Undesirable effects" Guidance in PL Section 2, What you need to know before you use Bortezomib Fresenius Kabi and section 4 "Possible side effects"	- Single AE report analysis, - Signal detection, Aggregate Reports - Review in PSURs
Pericardial disease	Guidance in SmPC section 4.4 "Special warnings and precautions for use" Listed in SmPC section 4.8 "Undesirable effects" Guidance in PL section 2 "What you need to know before you use Bortezomib" and section 4 "Possible side effects"	- Single AE report analysis, - Signal detection, Aggregate Reports - Review in PSURs
Pulmonary hypertension	Guidance in SmPC section 4.8 "Undesirable effects" Guidance in PL section 2 "What you need to know before you use Bortezomib" and section 4 "Possible side effects"	- Single AE report analysis, - Signal detection, Aggregate Reports - Review in PSURs
Herpes zoster infection	Guidance in SmPC section 4.4 "Special warnings and precautions for use" Listed in SmPC section 4.8 "Undesirable effects" Guidance in PL section 2 "What you need to know before you use Bortezomib" and section 4 "Possible side effects"	- Single AE report analysis, - Signal detection, Aggregate Reports - Review in PSURs
Posterior reversible encephalopathy syndrome	Guidance in SmPC section 4.4 "Special warnings and precautions for use" Listed in SmPC section 4.8 "Undesirable effects" Guidance in PL section 4 "Possible side effects"	- Single AE report analysis, - Signal detection, Aggregate Reports - Review in PSURs

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Optic neuropathy and different degrees of visual impairment (up to blindness)	Guidance in SmPC section 4.4 "Special warnings and precautions for use" Listed in SmPC section 4.8 "Undesirable effects" Guidance in PL section 2 "What you need to know before you use Bortezomib" and section 4 "Possible side effects"	- Single AE report analysis, - Signal detection, Aggregate Reports - Review in PSURs - Targeted follow-up questionnaires (Annex 4)
Thrombocytopenia and thrombocytopenia with associated bleeding	Guidance in SmPC section 4.2 "Posology and method of administration", 4.4 "Special warnings and precautions for use" and 4.9 "Overdose" Listed in SmPC section 4.8 "Undesirable effects" Guidance in PL section 2 "What you need to know before you use Bortezomib" and section 4 "Possible side effects"	- Single AE report analysis, - Signal detection, Aggregate Reports - Review in PSURs
Neutropenia and neutropenia with associated infection	Guidance in SmPC section 4.2 "Posology and method of administration", 4.4 "Special warnings and precautions for use" and 4.9 "Overdose" Listed in SmPC section 4.8 "Undesirable effects" Guidance in PL section 2 "What you need to know before you use Bortezomib" and section 4 "Possible side effects"	- Single AE report analysis, - Signal detection, Aggregate Reports - Review in PSURs
Important Potential Risks		
Progressive multifocal leukoencephalopathy	Guidance in SmPC section 4.4 "Special warnings and precautions for use", Listed in SmPC section 4.8 "Undesirable effects" Guidance in PL section 2 "What you need to know before you use Bortezomib" and section 4 "Possible side effects"	- Single AE report analysis, - Signal detection, Aggregate Reports - Review in PSURs - Targeted follow-up questionnaires (Annex 4)
Ventricular rhythm abnormalities	Listed in SmPC section 4.8 "Undesirable effects" Guidance in PL section 2 "What you need to know before you use Bortezomib" and section 4 "Possible side effects"	- Single AE report analysis, - Signal detection, Aggregate Reports - Review in PSURs

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Guillain-Barre syndrome	Listed in SmPC section 4.8 "Undesirable effects" Guidance in PL section 2 "What you need to know before you use Bortezomib" and section 4 "Possible side effects"	- Single AE report analysis, - Signal detection, Aggregate Reports - Review in PSURs
Other central nervous system disorders	Listed in SmPC section 4.8 "Undesirable effects" Guidance in PL section 2 "What you need to know before you are given bortezomib Kabi" and PL section 4 "Possible side effects"	- Single AE report analysis, - Signal detection, Aggregate Reports - Review in PSURs
Medication/dispensing errors	Guidance in SmPC section 4.2 "Posology and method of administration" Guidance in PL section 2 "What you need to know before you are given bortezomib Kabi" and PL section 4 "Possible side effects" Additional routine risk minimisation measures (Annex 6): • Education of HCP; reconstitution, dosing and administration booklet, reconstitution poster; dosing slide rule; training of medical representative • Proper training of all medical science liaison (MSL) or equivalent, on the different bortezomib treatment schedules approved for transplant induction • An educational programme and specific tools for HCPs who are involved in the prescription and administration of bortezomib combination regimens in the transplant induction	- Single AE report analysis, - Signal detection, Aggregate Reports - Review in PSURs - Targeted follow-up questionnaires (Annex 4)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing Information		
Safety in patients with cardiac impairment or with NYHA Class III or IV impairment	Guidance in SmPC section 4.2 "Posology and method of administration" and section 4.4 "Special warnings and precautions for use", Guidance in PL section 2 "How to use Bortezomib Fresenius Kabi "	- Single AE report analysis, - Signal detection, Aggregate Reports - Review in PSURs
Safety in patients with ECOG>2	Guidance in SmPC section 4.2 "Posology and method of administration" Guidance in PL section 2 "How to use Bortezomib Fresenius Kabi "	- Single AE report analysis, - Signal detection, Aggregate Reports - Review in PSURs
Second primary malignancies with BzTD induction therapy	Guidance in SmPC section 4.2 "Posology and method of administration"	- Single AE report analysis, - Signal detection, Aggregate Reports - Review in PSURs - Targeted follow-up questionnaires (Annex 4)

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Carboplatin 10 mg/ml concentrate for solution for infusion for visual analysis and Velcade 3.5 mg powder for solution for injection for content analysis. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of bortezomib, 3.5 mg powder for solution for injection. The reference product Velcade is indicated for :

Velcade 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.

Velcade 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.

Velcade 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.

Velcade 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.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Bortezomib Fresenius Kabi is favourable in the following indication:

- Bortezomib Fresenius Kabi 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 Fresenius Kabi 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 Fresenius Kabi 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 Fresenius Kabi 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,

and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

In each Member State, the Marketing Authorisation Holder (MAH) shall agree the content and format of the educational material with the national competent authority.

The MAH shall ensure that all healthcare professionals involved in the prescribing, dispensing, handling or administration of Bortezomib Fresenius Kabi are provided with educational material.

The educational material shall consist of the following:

- SmPC
- Reconstitution, dosing and administration booklet
- Reconstitution poster
- Dosing Slide Rule
- Induction Transplant Regimens Graph.

The Reconstitution, dosing and administration booklet shall contain the following key elements:

- Bortezomib Fresenius Kabi 3.5 mg can be administered both intravenously and subcutaneously, while Bortezomib Fresenius Kabi 1 mg can be administered only intravenously
- different reconstitution requirements for intravenous or subcutaneous use
- dosing instructions and examples: how to calculate the body surface area of a patient and the volume of reconstituted Bortezomib Fresenius Kabi (both intravenous and subcutaneous use) required for different body surface areas (cross reference to Dosing Slide Rule)

- advice on method of administration for both intravenous and subcutaneous use, including the need to rotate injection sites for subcutaneous use
- storage precautions for reconstituted solution
- potential risks of administration errors including overdosing, underdosing and that inadvertent intrathecal administration has resulted in death
- to report any adverse event, or medication error experienced with the administration of Bortezomib Fresenius Kabi.

The Reconstitution poster shall contain the following key elements:

- different reconstitution requirements for Bortezomib Fresenius Kabi 3.5 mg intravenous or subcutaneous use
- need to handling the medicinal product in sterile setting
- storage precautions for reconstituted solution
- advice on how to reduce the risk of mix-up of intravenous and subcutaneous reconstituted syringes
- that Bortezomib Fresenius Kabi is to be given only by intravenous or subcutaneous injections; no other route of administration is allowed
- that Bortezomib Fresenius Kabi 1 mg is only for intravenous use
- to report any adverse event, or medication error experienced with the administration of Bortezomib Fresenius Kabi.

Dosing Slide Rule shall contain the following key elements:

- a dose-calculation tool that enables prescribers to input a patient's height and weight in order to calculate the body surface area (BSA) and thereby to determine the appropriate Bortezomib Fresenius Kabi dose.
- different reconstitution requirements for intravenous or subcutaneous use
- dosing instructions and examples: how to calculate the body surface area of a patient and the volume of reconstituted Bortezomib Fresenius Kabi (both intravenous and subcutaneous use) required for different body surface areas.

Induction Transplant Regimens Graph shall contain the following key elements:

- instructions for prescribing and administration including the cycles' length and number of cycles, to minimise the risk of medication and dispensing errors potentially induced by the existence of the two different bortezomib combination regimens in the Transplant Induction Setting (Bortezomib Fresenius Kabi plus dexamethasone, and Bortezomib Fresenius Kabi plus dexamethasone and thalidomide).
- to remind that patients receiving Bortezomib Fresenius Kabi in combination with thalidomide should adhere to the pregnancy prevention programme of thalidomide, with reference to the SmPC of thalidomide for additional information.