EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bortezomib SUN

International non-proprietary name: bortezomib

Procedure No. EMEA/H/C/004076/0000

Note

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

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List of abbreviations

ASMF	Active Substance Master File = Drug Master File
CHMP	Committee for Human Medicinal Products
CQA	Critical Quality Attribute
EC	European Commission
ERA	Environmental Risk Assessment
EU	European Union
GC	Gas Chromatography
GMP	Good Manufacturing Practice
HCP	Healthcare Professional
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPQC	In-Process Quality Control
IR	Infrared
IV	Intravenous
LCMS	Liquid Chromatography Mass Spectrometry
LDPE	Low density polyethylene
LoD	Loss on Drying
MAH	Marketing Authorisation Holder
NLT	Not less than
NMR	Nuclear Magnetic Resonance
PRAC	Pharmacovigilance Risk Assessment Committee
Ph. Eur.	European Pharmacopoeia
QTPP	Quality Target Product Profile
RH	Relative Humidity
SC	Subcutaneous
SmPC	Summary of Product Characteristics
TGA	Thermo-Gravimetric Analysis

UPLC	Ultra-Performance Liquid Chromatography
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National formulary
UV	Ultraviolet
WFI	Water For Injection

1. Background information on the procedure

1.1. Submission of the dossier

The applicant SUN Pharmaceutical Industries (Europe) B.V. submitted on 2 March 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Bortezomib SUN, 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 September 25th, 2014.

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 for which a Marketing Authorisation is or has been granted in the Union on 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 SUN 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 SUN 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 SUN 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.

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 instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community 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 Community/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

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 (Appendix 1).

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Ines Baotic

- The application was received by the EMA on 2 March 2015.
- The procedure started on 25 March 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on 12 June 2015.
- The PRAC Rapporteur's Risk Management Plan (RMP) Assessment Report was endorsed by PRAC on 9 July 2015.
- During the meeting on 23 July 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The consolidated List of Questions was sent to the applicant on 23 July 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 27 November

2015.

- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP and PRAC members on 4 January 2016.
- The PRAC Rapporteur's Risk Management Plan (RMP) Assessment Report was endorsed by PRAC on 14 January 2016.
- During the CHMP meeting on 28 January 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 2 March 2016.
- The Rapporteur circulated the Assessment Report and the Similarity Report on the applicant's responses to the List of Outstanding Issues to all CHMP and PRAC members on 11 March 2016.
- The PRAC Rapporteur's Risk Management Plan (RMP) Assessment Report was endorsed by PRAC on 17 March 2016.
- During the CHMP meeting on 1 April 2016, the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 25 April 2016.
- The Rapporteur circulated the Assessment Report and the updated Similarity Report on the applicant's responses to the 2nd List of Outstanding Issues to all CHMP and PRAC members on 4 May 2016.
- The CHMP adopted an Assessment Report on similarity for Bortezomib SUN with Revlimid, Thalidomide Celgene, Imnovid, Farydak, Krypolis, Imbruvica, Torisel and Darzalex on the 26 May 2016.
- During the meeting on 26 May 2016, 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 SUN.

2. Scientific discussion

2.1. Introduction

This application for a marketing authorisation concerns a generic application of a Centrally Authorised Medicinal Product according to article 10(1) for Bortezomib SUN 3.5 mg powder for solution for injection. The reference product is Velcade 3.5 mg powder for solution for injection which has been authorised in the EU since 26th April 2004 through centralised procedure by Janssen-Cilag International NV.

Bortezomib is a highly selective, reversible inhibitor of 26S proteasome in mammalian cells, a large protein complex that degrades ubiquinated proteins. Inhibition of the 26S proteasome prevents this 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 applicant requested the approval 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.

The final indication following CHMP review of this application is: Bortezomib SUNas 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 SUN 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 SUN 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 SUN 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 SUN 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 of bortezomib (as mannitol boronic ester) as active substance.

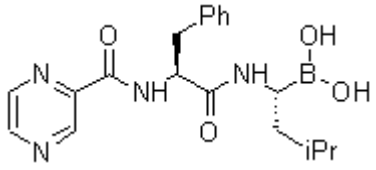
The only other ingredient is mannitol.

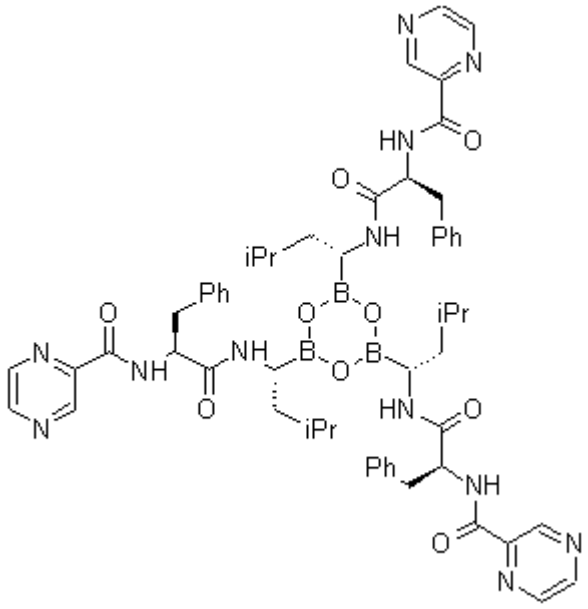
The product is available in type I glass vials with grey bromobutyl rubber stoppers, sealed with light green flip off aluminium seals as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

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 $C_{19}H_{25}BN_4O_4$ and it has a relative molecular mass of 384.24 g/mol. It is isolated in its trimeric form which has the chemical name 2,4,6-tri- [(1*R*)-3-methyl-1-[[(2*S*)-1-oxo-3-phenyl-2-(pyrazinylcarbonyl)amino]propyl]amino] butyl] - 1,3,5,2,4,6-trioxatriborinane, the molecular formula $C_{57}H_{69}B_3N_{12}O_9$ and a relative molecular mass of 1098.67 g/mol. Bortezomib and its trimeric form have the following structures:





The chemical structure of bortezomib trimer was inferred from its route of synthesis and confirmed by infrared spectroscopy, ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy, ultraviolet spectroscopy, mass spectrometry and elemental analysis. Spectra were recorded in aprotic solvents to distinguish between monomeric and trimeric forms as the boroxine is labile in protic solvents.

The active substance is a white to light brown hygroscopic crystalline powder, slightly soluble in water and soluble in methanol.

Bortezomib contains two chiral centres. Diastereomers are controlled by HPLC whilst the amount of enantiomer is tested by a chiral HPLC method, all in the active substance specification. The active substance is routinely isolated as the same polymorphic form which was shown to be stable during stability studies. The active substance is fully dissolved and lyophilised with mannitol, generating the mannitol ester, during finished product manufacture so polymorphic form of the active substance is not important for finished product performance and is not routinely controlled.

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. A single source of active substance is used although two manufacturers are used, responsible for different steps.

Bortezomib is synthesized in four main steps using well defined starting materials with acceptable specifications. One originally-proposed starting material was re-defined during the procedure at the request of CHMP to ensure that enough of the process is conducted under GMP. One chiral centre originates in a starting material, whilst the other is generated during the process using a chiral auxiliary approach. Crystallisation under anhydrous conditions ensures the trimeric form of the active substance is isolated.

Adequate in-process controls are applied during the synthesis. 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.

The active substance is doubly packaged in LDPE bags under nitrogen with silica gel desiccant, inside a further two aluminium polyaminated bags. These are stored in a black LDPE bag inside a fibre drum. The materials comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, solubility (Ph. Eur.), identity (IR, UPLC, colour test for boron, LCMS), loss on drying (TGA), residual solvents (GC), impurities (UPLC, HPLC, GC), assay (UPLC), clarity of solution (in-house), colour index (in-house), bacterial endotoxins (Ph. Eur.) and bioburden (Ph. Eur.).

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 on three production scale batches of the active substance were provided. The results were within the specifications and consistent from batch to batch.

Stability

Stability data on three production scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (-20±5 ºC) and for up to 6 months under accelerated conditions (5±3 ºC) according to the ICH guidelines were provided. The following parameters were tested: description; identification; LoD; related substances; assay; colour and clarity of

solution; bacterial endotoxins and bioburden. The analytical methods used were the same as for release. All tested parameters remained within specification for the duration of the studies.

Photostability testing following the ICH guideline Q1B was performed on one batch. Bortezomib is sensitive to light and should be stored in the proposed container in order to prevent photo-degradation. Forced degradation studies were carried out by exposing one batch to heat or in solution, to acid, alkali and oxidative conditions. Bortezomib is relatively heat stable but degrades under the other conditions, especially oxidatively. These studies demonstrate that the impurities methods are stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months at -20±5 ºC in the proposed container, which has been shown to provide sufficient protection from light.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Bortezomib SUN is a sterile white to off-white lyophilized powder for solution for injection containing the active substance and mannitol. The aim was to develop a qualitatively and quantitatively identical formulation to Velcade which is a lyophilized powder for intravenous or subcutaneous administration. As such, no bioequivalence study was needed. Like the reference product, the active substance is isolated in its trimeric form which hydrolyses to the monomer on dissolution in water, and then forms a mannitol ester on addition of mannitol followed by freeze drying. The various bortezomib forms have been evaluated by structural characterization data.

A lyophilization process was chosen akin to the reference product to ensure a similar cake is produced. Sterile filtration and aseptic filling were chosen rather than terminal sterilization given the instability of the active substance to heat. In order to prevent degradation due to contact with the vessel and tubing, bulk solution holding times are defined.

Initially, the applicant miscalculated the amount of trimer required to generate the same strength of product as Velcade, resulting in a product which contained 5% more active substance. This major objection was resolved by manufacturing new batches using the correct amount of bortezomib trimer and providing new assay data during the procedure. Formulae for calculating the requisite amount of active substance have been revised and adequately justified.

The applicant has applied QbD principles in the development of the finished product and its manufacturing process. The quality target product profile (QTPP) was defined as a lyophilized powder in a suitable container with a shelf-life of at least 36 months at room temperature and pharmaceutically equivalent to Velcade. Potential critical quality attributes (CQAs) were then assessed based on likelihood of impacting patient safety. These were then defined as identity, assay (bortezomib and mannitol), impurities, uniformity of dosage units, water content, clarity, completeness and pH of reconstituted solution, bacterial endotoxins and particulate matter. Only those CQAs liable to be impacted by process variables were monitored during development.

The potential impact of active substance quality attributes on the CQAs of the finished product was assessed using a risk-based approach. The specification of the active substance ensures no adverse impact. Manufacturing process parameters were then investigated, again using a risk-based approach for prioritization. In order to ensure complete dissolution and thus a uniform finished product, a mixture of water

and *tert*-butanol is used. Oxygen is excluded and temperature limited to avoid degradation. Process parameters were set for the various operations in order to ensure the quality of the finished product. However, no multivariate studies were undertaken and no design space is claimed.

All excipients are well known pharmaceutical ingredients and their 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.

The primary packaging is a type 1 glass vial with bromobutyl rubber stopper and flip-off aluminium seal. 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 five main steps: compounding, sterile filtration, aseptic filling, lyophilisation and sealing. The process is considered to be a non-standard manufacturing process due to the aseptic processing. The process is carried out under nitrogen and diffused light at controlled temperature given the sensitivity of the active substance.

Major steps of the manufacturing process were validated on three successive production scale batches of Bortezomib SUN, produced using the previously incorrect batch formula. Given the simplicity of the formulation and the likely minor impact of the change on process performance, re-validation of the corrected process was not considered necessary. 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 are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications are appropriate for this kind of dosage form and include tests for appearance, identity (UV, UPLC), water content (Ph. Eur.), constitution time (in-house), clarity, completeness, pH and osmolarity of constituted solution (USP and in-house), particulate matter (Ph. Eur.), sterility (Ph. Eur.), uniformity of dosage units (Ph. Eur.), related substances (UPLC), mannitol assay (HPLC) and assay (UPLC).

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 three production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data for three 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. Samples were tested for description, identification, water content, reconstitution time, clarity, completeness, pH and osmolarity of reconstituted solution, particulate matter, sterility, related substances and assay. The analytical procedures used are stability indicating.

The batches of medicinal product contain 5% more active substance than those planned for marketing due to the miscalculation in the batch formula. However, given that the only difference is the amount of active substance, they were packed in the primary packaging proposed for marketing and that there were no

significant trends to any of the measured parameters throughout the study period, they are considered representative. Additional stability studies using batches containing the correct amount of active substance have been started.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Although the active substance is photosensitive, the finished product, stored in its commercial pack, is not susceptible to light-induced degradation which demonstrates the protective nature of the packaging.

A temperature cycling study was undertaken to evaluate stability during shipping and handling. Samples were stored between -20 and 40 ^{o}C alternatively over a four week period without detriment to the quality of the finished product, thus demonstrating it is robust to the variations in temperature encountered during shipping and handling operations.

A reconstitution stability study was also carried out using 0.9% NaCl solution as per the SmPC. Solutions (1 and 2.5 mg/ml) were stored in the original vial and in sterile syringes at 25 ^{o}C demonstrating in-use stability for up to 8 hours, without protection from light. The applicant committed to repeat the study on a batch near the end of its shelf-life.

Based on available stability data, the proposed shelf-life of 12 months in the commercial pack, with the vials inside the carton to protect from light, without special temperature storage conditions as stated in the SmPC (section 6.3) is acceptable.

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 applicant has applied QbD principles in the development of the finished product and its manufacturing process although no design space or regulatory flexibility is claimed. 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 objection on starting materials was resolved by re-definition. The major objection relating to the incorrect calculation of active substance was also resolved by manufacturing new batches. It was considered that the change on composition was unlikely to affect manufacturing parameters or stability of the product.

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

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- Stability studies on the new batches of Bortezomib SUN manufactured using the correct amount of active substance should be carried out for the duration of the shelf-life.
- The reconstitution stability study should be repeated on a batch near the end of its shelf-life.

2.3. Non-clinical aspects

2.3.1. Introduction

The applicant did not submit non-clinical data with this application. 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 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.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Bortezomib SUN manufactured by Sun pharmaceuticals Industries Europe B.V. 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 and not increased.

2.3.3. Discussion and conclusion 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 lack of non-clinical studies based on the literature review and the claim that Bortezomib SUN 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 SUN in the applied indications.

2.4. Clinical aspects

2.4.1. Introduction

The Applicant has not conducted clinical pharmacology, efficacy and safety studies with Bortezomib SUN 3.5 mg powder for solution for injection. The relevant SmPC sections of Bosterzomib SUN are in line with the SmPC of the reference product VELCADE.

Exemption

The Applicant states that Bortezomib SUN 3.5 mg powder for solution for injection has identical composition as the reference medicinal product (it contains the same active substance in the same concentration as the brand leader Velcade 3.5 mg powder for solution for injection).

According to the CHMP Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), 20 January 2010, Appendix II, a biowaiver for a parenteral solution can be accepted provided it is administered as an aqueous intravenous solution containing the same active substance as the currently approved reference product and excipients do not interact and/or otherwise affect the disposition of the drug substance. In the case of other parenteral routes, e.g. intramuscular or subcutaneous, and when the test product is of the same type of solution, contains the same concentration of the same active substance and the same excipients in similar amounts as the medicinal product currently approved, bioequivalence studies are 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

Based on the submitted data it can be concluded that Bortezomib SUN 3.5 mg powder for solution for injection has the same pharmaceutical form, route of administration and strength as VELCADE 3.5 mg powder for solution for injection. According to the current Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98/Rev1) no bioequivalence studies are needed for this type of application.

During the assessment, the applicant submitted an updated clinical overview to add the new indication, which was approved during the procedure: 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 SmPC has been updated with the new indication.

2.4.6. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Bortezomib SUN 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

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

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

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 1.2 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Heart failure Hepatotoxicity Acute hypersensitivity reaction Tumour lysis syndrome Peripheral motor neuropathy (including paralysis) Autonomic neuropathy Acute diffuse infiltrative pulmonary disease Pericardial disease Pulmonary hypertension Herpes zoster virus infection Posterior reversible encephalophathy syndrome Optic neuropathy and different degrees of visual impairment (up to blindness) Thrombocytopenia and thrombocytopenia with associated bleeding Neutropenia and neutropenia with associated infection
Important potential risks	Progressive multifocal leukoencephalopathy

Summary of safety concerns	
	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 bortezomib, thalidomide and dexamethasone induction therapy

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Heart failure	Information on this safety concern is provided in following sections of SmPC: 4.4 and 4.8 Prescription only medicine.	None proposed
Hepatotoxicity	Information on this safety concern is provided in following sections of SmPC: 4.2, 4.4 and 4.8 Prescription only medicine.	None proposed
Acute hypersensitivity reaction	Information on this safety concern is provided in following sections of SmPC: 4.3, 4.8 and 6.1 Prescription only medicine.	None proposed
Tumour lysis syndrome	Information on this safety concern is provided in following sections of SmPC: 4.4 and 4.8 Prescription only medicine.	None proposed.
Peripheral motor neuropathy (including	Information on this safety concern is provided in following sections of SmPC:	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
paralysis)	4.2, 4.4 and 4.8 Prescription only medicine.	
Autonomic neuropathy	Information on this safety concern is provided in following sections of SmPC: 4.4 and 4.8 Prescription only medicine.	None proposed.
Acute diffuse infiltrative pulmonary disease	Information on this safety concern is provided in following sections of SmPC: 4.3, 4.4 and 4.8 Prescription only medicine.	None proposed.
Pericardial disease	Information on this safety concern is provided in following sections of SmPC: 4.3 and 4.8 Prescription only medicine.	None proposed.
Pulmonary hypertension	Information on this safety concern is provided in section 4.8 of SmPC. Prescription only medicine.	None proposed.
Herpes zoster virus infection	Information on this safety concern is provided in following sections of SmPC: 4.2, 4.4 and 4.8 Prescription only medicine.	None proposed.
Posterior reversible encephalopathy syndrome	Information on this safety concern is provided in following sections of SmPC: 4.4 and 4.8 Prescription only medicine.	None proposed.
Optic neuropathy and different degrees of visual impairment (up to blindness)	Information on this safety concern is provided in following sections of SmPC: 4.3 and 4.8 Prescription only medicine.	None proposed.
Thrombocytopenia and thrombocytopenia with associated bleeding	Information on this safety concern is provided in following sections of SmPC: 4.2, 4.4 and 4.8 Prescription only medicine.	None proposed.
Neutropenia and	Information on this safety concern is	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
neutropenia with associated infection	provided in following sections of SmPC: 4.2, 4.4 and 4.8 Prescription only medicine.	
Progressive multifocal leukocencephalopathy	Information on this safety concern is provided in section 4.4 of SmPC. Prescription only medicine.	None proposed.
Ventricular rhythm abnormalities	Information on this safety concern is provided in following sections of SmPC: 4.4 and 4.8 Prescription only medicine.	None proposed.
Guillain-Barré syndrome	Currently the available data does not support the need for risk minimisation measures. Prescription only medicine.	None proposed.
Other central nervous system disorders	Information on this safety concern is provided in following sections of SmPC: 4.2, 4.4 and 4.8 Prescription only medicine.	None proposed.
Medication/dispensing errors	<u>Medication error related to route of administration IV vs SC administration</u> Information on this safety concern is provided in following sections of SmPC: 4.2, 4.4, 4.6 and 6.6 Prescription only medicine.	As part of Bortezomib Educational Programme following educational materials will be supplied to the HCPs, pharmacists and other specialised healthcare personnel involved in prescribing, dispensing and/or reconstitution of Bortezomib SUN: • Reconstitution, Dosing and Administration Booklet • Reconstitution poster • Dosing Slide Rule
	<u>Medication error due to confusion with administering the incorrect regimens in the transplant induction setting</u> Information on this safety concern is provided in following sections of SmPC: 4.2 and 4.8	As part of Transplant Induction Setting Additional Educational Programme the 'Induction Transplant Regimens Graph' will be supplied to HCPs, and other specialised healthcare personnel involved in prescribing and administration of Bortezomib SUN

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Prescription only medicine.	
Safety in patients with cardiac impairment or with NYHA Class III or IV impairment	Information on this safety concern is provided in section 4.4 of SmPC. Prescription only medicine.	None proposed.
Safety in patients with ECOG>2	Currently the available data does not support the need for risk minimisation measures. Prescription only medicine.	None proposed.
Second primary malignancies with bortezomib, thalidomide and dexamethasone induction therapy	Information on this safety concern is provided in following sections of SmPC: 4.4 and 4.8 Prescription only medicine.	None proposed.

2.6. PSUR submission

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. 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.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

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.

A bioequivalence study was not submitted and this was considered acceptable. Bortezomib SUN contains the same active ingredient and excipients in the same concentration and pharmaceutical formulation using the same route of administration (parenteral) as for the reference product. The results of tests carried out indicate consistency and uniformity of the important product quality characteristics for Bortezomib SUN, hence, the quality of this product is considered to be acceptable.

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.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

Therefore, the benefit risk balance for Bortezomib SUN is considered positive.

4. Recommendation

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Bortezomib SUN is not similar to Revlimid (lenalidomide), Thalomide Celgene (thalidomide), Imnovid (pomalidomide), Farydak (panobinostat), Kyprolis (carfilzomib), Darzalex (daratumumab), Imbruvica (ibrutinib) and Torisel (temsirolimus), within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Bortezomib SUN in the following indications:

- Bortezomib SUN 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 SUN 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 SUN 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 SUN 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,

is favourable 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).

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 SUN are provided with educational materials.

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 SUN 3.5 mg can be administered both intravenously and subcutaneously
- different reconstitution requirements for intravenous (IV) or subcutaneous (SC) use
- dosing instructions and examples: how to calculate the body surface area of a patient and the volume of reconstituted Bortezomib SUN (both IV and SC use) required for different body surface areas (cross reference to Dosing Slide Rule)
- advice on method of administration for both IV and SC use, including the need to rotate injection sites for SC 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 SUN 3.5 mg.

The Reconstitution poster shall contain the following key elements:

- different reconstitution requirements for Bortezomib SUN 3.5 mg IV or SC 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 IV and SC reconstituted syringes
- that Bortezomib SUN is to be given only by IV or SC injections; no other route of administration is allowed
- to report any adverse event, or medication error experienced with the administration of Bortezomib SUN 3.5 mg.

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 SUN dose.

- different reconstitution requirements for intravenous (IV) or subcutaneous (SC) use
- dosing instructions and examples: how to calculate the body surface area of a patient and the volume of reconstituted Bortezomib SUN (both IV and SC 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 SUN plus dexamethasone, and Bortezomib SUN plus dexamethasone and thalidomide).
- to remind that patients receiving Bortezomib SUN in combination with thalidomide should adhere to the pregnancy prevention programme of thalidomide, with reference to the SmPC of thalidomide for additional information.

- **Obligation to conduct post-authorisation measures**

Not applicable.