26 May 2016
EMA/CHMP/421198/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bortezomib Hospira

International non-proprietary name: bortezomib

Procedure No. EMEA/H/C/004207/0000

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
ERA	Environmental Risk Assessment
GC	Gas Chromatography
HCP	Healthcare Professional
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
IR	Infrared
IV	Intravenous
LDPE	Low density polyethylene
NLT	Not less than
NMR	Nuclear Magnetic Resonance
PRAC	Pharmacovigilance Risk Assessment Committee
Ph. Eur.	European Pharmacopoeia
RH	Relative Humidity
SC	Subcutaneous
SmPC	Summary of Product Characteristics
TGA	Thermo-Gravimetric Analysis
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 Hospira UK Limited submitted on 14 September 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Bortezomib Hospira, 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 23 April 2015.

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 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 Hospira 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 Hospira 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 Hospira 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 Hospira 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 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 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, Belgium
- 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, Belgium
- 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.

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: Milena Stain

- The application was received by the EMA on 14 September 2015.
- The procedure started on 1 October 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 December 2015.
- During the meeting on 28 January 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 25 February 2016.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 5 April 2016.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 16 April 2016.

- During the CHMP meeting on 28 April 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 3 May 2016.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the consolidated List of Outstanding Issues to all CHMP members on 11 May 2016.
- The CHMP adopted an Assessment Report on similarity for Bortezomib Hospira with Revlimid, Thalidomide Celgene, Imnovid, Farydak, Krypolis, Imbruvica, Torisel and Darzalex on 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 Hospira.

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 Hospira 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, a dipeptidyl boronic acid derivative, is a highly selective and reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome subunit in mammalian cells. Inhibition of the proteasome results in cell cycle arrest and apoptosis. 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 Velcade 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 Hospira 3.5 mg powder for solution for injection can be used for either subcutaneous or intravenous 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.

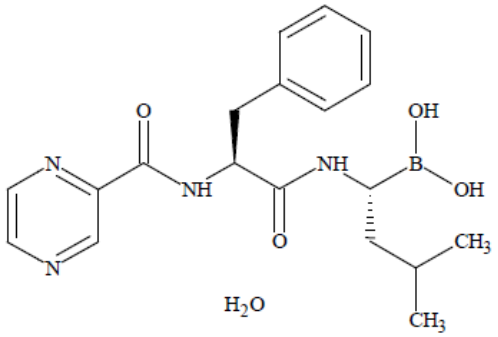
The other ingredient is mannitol.

The product is available in type 1 glass 10 ml vial with a rubber stopper and an aluminium seal as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of bortezomib is [(1R)-3-methyl-1-[[(2S)-3-phenyl-2-(pyrazine-2 carbonylamino) propanoyl]amino]butyl] boronic acid, and has the following structure and properties:



Formula: $C_{19}H_{25}BN_4O_4.H_2O$ Molecular weight: 402.24 g/mol

Figure 1. Chemical structure of bortezomib.

The chemical structure of bortezomib was confirmed by elemental analysis (C, H, N), mass spectrometry, ^{1}H and ^{13}C NMR, IR spectroscopy, UV spectroscopy, identification by HPLC (retention time), single crystal X-ray diffraction and powder X-ray diffraction.

The active substance is a white to off-white crystalline powder, slightly hygroscopic, practically insoluble in water.

Bortezomib contains two chiral centres and diastereomer/enantiomeric content is controlled routinely by HPLC. The active substance shows polymorphism and it has been confirmed by XRD that the polymorphic form produced by the proposed manufacturer is a novel for . Bortezomib is fully dissolved and lyophilised with mannitol during finished product manufacturing process, therefore polymorphic form is not considered to be important for finished product performance.

Manufacture

Bortezomib is produced by one manufacturer in seven convergent steps from three well defined starting materials with suitable specifications. One chiral centre originates in one of the starting materials whilst the other is introduced selectively during the process. Stereoisomeric impurities are controlled both by testing the relevant starting material and intermediate, and in the active substance specification. Polymorphic form is adequately controlled by the final crystallisation step.

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.

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

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

The active substance is packaged in a transparent low-density polyethylene (LDPE) bag purged with nitrogen and tied with strip seal. This bag is placed in another transparent LDPE bag which contains a silica gel bag and is strip sealed. This double transparent LDPE bag is further placed in a triple laminated Sunlight Barrier (TLSB) bag and heat sealed. Subsequently, this triple laminated bag is placed into high density polyethylene drum (HDPE). The LDPE bags comply with the EC regulation 10/2011 and amendments for plastic materials and the Ph. Eur. monograph 3.1.3. Polyolefins.

Specification

The active substance specification includes tests for description, identification (IR, HPLC), appearance of solution, water content (KF oven), chiral purity (HPLC), assay (HPLC), related substances (HPLC), residual solvents (GC), sulphated ash (Ph. Eur.) , heavy metals (Ph. Eur., USP), bacterial endotoxins (Ph. Eur.) and microbial limits (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 the active substance and impurities has been presented.

Batch analysis data on nine production scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on four commercial scale batches of active substance from the proposed manufacturers packaged in the container closure system intended for the market and stored for up to 24 months under long term conditions (-20°C±5°C) and for up to 6 months under accelerated conditions (5±3°C), according to the ICH guidelines, were provided.

The following parameters were tested: description, appearance of solution, identification (IR), water content (coulometer or TGA), diastereomer/enantiomer content (HPLC), related substances (HPLC), assay (HPLC) and bacterial endotoxins.

No significant changes to any of the measured parameters were observed under long term or accelerated conditions.

Forced degradation studies including acid and base hydrolysis, oxidation, thermal degradation and photolysis were also performed, indicating that bortezomib was unstable under all conditions tested. The results from this study demonstrated that the proposed methods for assay, enantiomer and related substances are stability indicating and suitable for their intended use, and that the active substance should be stored protected from light.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period when stored in the proposed container closure system.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product Bortezomib Hospira is a sterile, lyophilized powder for solution for injection which contains 3.5 mg of the active substance bortezomib (as a mannitol boronic ester) per vial intended for dilution with 0.9% sodium chloride prior to administration.

The aim of the pharmaceutical development was to develop a finished product equivalent to Velcade. The formulation of Bortezomib Hospira was based on the reference medicinal product.

The only excipient present in the finished product is mannitol (bulking agent). 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 2.2.1 of this report. Since the excipients selected are the same used for the reference medicinal product, no excipient compatibility studies were performed.

Although different forms of bortezomib are used for the manufacture of the reference medicinal product (trimeric anhydride form) and generic medicinal product (monohydrate form), since the active substance is dissolved during compounding, both forms dissociate and exist as the same species: bortezomib free acid. This is followed by a conversion to a boronic ester (a 'di-ester') with mannitol during lyophilization. Therefore, the form present in both finished products is the same, which has been supported by comparative batch analysis data, supplemented by NMR identification analysis. No differences were identified irrespective of concentration or storage conditions, and the ratio of bound to unbound bortezomib was the same in Velcade and Bortezomib Hospira's samples.

During formulation development a risk assessment of the formulation variables against finished product critical quality attributes (CQAs) was conducted. Acceptable ranges for the high and medium risk formulation variables were established and included in the control strategy.

The CQAs of the finished product have been adequately investigated by development studies and are controlled by tests and specifications.

During pharmaceutical development, analysis of reference medicinal product batches determined the concentration of bortezomib and mannitol to be used the bulk solution prior to lyophilisation. This information was also used when assessing the thermal properties of both the active substance and finished product bulk solution to determine the lyophilisation conditions.

The stability of the bulk formulation was assessed at different storage conditions. The data obtained demonstrated that the bulk solution can be stored at the proposed storage conditions. A series of risk assessments were conducted to better understand the manufacturing process and to develop a control strategy to reduce the risk of a failed batch. The risks of critical process variables was reduced to an acceptable level and controlled in the finished product by specified parameters.

The applicant performed a study of the photostability of the active substance to determine if any special precautions are required during product manufacture or storage. The results demonstrated that bortezomib active substance is stable under ambient lighting conditions for up to 24 hours.

Since Bortezomib Hospira is to be reconstituted with 0.9% sodium chloride prior to administration (1.0 mg/mL for intravenous use and 2.5 mg/mL for subcutaneous use), a compatibility study with the proposed reconstitution solution and the container closure system was also performed. Samples of Velcade and Bortezomib Hospira diluted to 1.0 and 2.5 mg/mL with 0.9% sodium chloride, stored under 25°C ± 2°C or 5°C ± 3°C for up to 24 hours were tested for description, pH, assay, related substances, particulate matter and reconstitution. The results demonstrated that the finished product reconstituted with 0.9% sodium chloride at both concentrations of 1.0 mg/mL and 2.5 mg/mL and stored in the original vial or syringe stored under those conditions is stable for 8 hours.

The primary packaging is type I glass 10 ml vial with a rubber stopper and an aluminium seal containing 3.5 mg bortezomib. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data. Container closure integrity studies and a study on potential extractables and leachables have been also performed. The integrity of the chlorobutyl elastomeric closure relative to the container clear glass vial has been ensured. The results confirm that the proposed primary packaging is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of six main steps: compounding, filtration, filling, lyophilization, sealing and packaging. The process is considered to be a non-standard manufacturing process. A detailed description of the manufacturing process of the finished product including the manufacture of the bulk solution, subsequent steps of the sterile filtration and respective in-process controls has been provided.

Major steps of the manufacturing process have been validated by a number of studies. 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.

Product specification

The finished product release specifications include appropriate tests for a sterile parenteral preparation and include: description, identification (HPLC, UV), pH (Ph. Eur.), assay (HPLC), related substances (HPLC), water content (Ph. Eur.), residual solvents (GC), uniformity of dosage units (Ph. Eur.), reconstitution time (visual), particulate matter (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.). The finished product is released on the market based on the above release specifications, through traditional final product release testing.

The proposed specifications are considered acceptable. Nevertheless, the CHMP recommends the revision of the limits for the parameter total impurities in the release and shelf-life finished product specification once additional long term stability data from commercial scale active substance and finished product batches becomes available.

The absence of a test for chiral impurity has been adequately justified based on batch analysis data on the active substance and corresponding finished product stored for six months under accelerated storage conditions (40°C/75%RH) demonstrating no increase in chiral impurities. The absence for a test for clarity and colour of solution has also been justified based on available stability data.

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 are provided for three commercial 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 of three commercial scale batches of finished product stored under long term conditions for 12 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

The batches of Bortezomib Hospira are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description of plug, description of reconstituted solution, pH, clarity of solution, color of solution, assay (HPLC), related substances (HPLC), water content (Ph. Eur.), residual solvents (GC), uniformity of dosage units (Ph. Eur.), reconstitution time (visual), particulate matter (Ph. Eur.), bacterial endotoxins (Ph. Eur.) and sterility (Ph. Eur.). The analytical procedures used are stability indicating. The vials were stored in upright and inverted positions.

All results of the stability study comply with the proposed shelf-life specification.

Stress studies on the finished product were performed by storing samples from three commercial scale batches in inverted position in a freezer (-15°C to -25°C) for 1 month. Results showed that the freeze-thaw conditions had no impact on the finished product since all attributes (appearance, pH, assay and related substances) remaining unchanged.

Forced degradation studies on one lab batch exposed to acid, base, heat, oxidation (H_2O_2) and light were also conducted. The data demonstrates that the product is only susceptible to degradation under harsh oxidative conditions.

In addition one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No detrimental effect on the appearance, reconstitution time or pH. No significant difference between the samples protected from light by either aluminum foil or cardboard carton was observed. However, the data showed significant degradation of the finished product after exposure for 10 days to accelerated lighting conditions, especially with an increase of impurities C and D. Therefore, a protection from light for long term storage has been proposed.

As indicated under pharmaceutical development, since Bortezomib Hospira is required to be reconstituted with 0.9% sodium chloride prior to administration (1.0 mg/mL for intravenous use and 2.5 mg/mL for subcutaneous use), a study to demonstrate the stability of the product upon reconstitution and storage for up to 8 hours, was conducted. Samples were tested for description, pH, assay, related substances and particulate matter. The results demonstrated that similarly to the reference medicinal product, the reconstituted product as described above, is stable for 8 hours in the original vial or syringe at room temperature (25°C ± 2°C) or under refrigeration (5°C ± 3°C).

Based on available stability data, the proposed shelf-life of 24 months with no special storage conditions as stated in the SmPC (section 6.3) are acceptable. 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. However, as indicated above, the chemical and physical in-use stability of the reconstituted solution has been demonstrated for 8 hours at 5°C and 25°C stored in the original vial and/or a syringe. The total storage time for the reconstituted medicinal product should not exceed 8 hours 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 different forms of bortezomib are used for the manufacture of the reference medicinal product (trimeric anhydride form) and the generic medicinal product (monohydrate form), and their lack of impact on the final finished product have been adequately addressed. It has been confirmed that the form present in both finished products is the same. 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.

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. Recommendation 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:

- To revise the limits for the parameter total impurities in the release and shelf-life finished product specification once additional long term stability data from commercial scale active substance and finished product batches becomes available.

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.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Bortezomib Hospira manufactured by Hospira UK Limited 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 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 Hospira 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 Hospira in the applied indications.

2.4. Clinical aspects

2.4.1. Introduction

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of bortezomib based on published literature. The relevant SmPC sections of Bosterzomib Hospira are in line with the SmPC of the reference product VELCADE.

Exemption

The marketing authorisation application (MAA) for Bortezomib Hospira 3.5 mg powder for solution for injection is based upon „essential similarity" to the original product (VELCADE 3.5 mg powder for solution for injection) in accordance with Article 10(1) of Directive 2001/83/EC, as amended.

The active drug substance (bortezomib), pharmaceutical form (powder for solution for injection), the strength (3.5 mg) and the route of administration (the lyophilised powder enables intravenous or subcutaneous administration after reconstitution) are the same for both products. The concentration (after reconstitution) is the same as those for VELCADE, and so are the indications applied for. In addition, the excipients are the same in very similar amounts.

Regarding the waiver of bioequivalence studies it is important to highlight that Bortezomib Hospira 3.5 mg powder for solution for injection is available for intravenous or subcutaneous administration. This corresponds to the mode of administration of the reference product (VELCADE 3.5 mg powder for solution for injection).

According 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. In the case of other parenteral routes, e.g. intramuscular or subcutaneous, and when the test product is of the same type of solution (aqueous or oily), 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" as well.

Bortezomib Hospira 3.5 mg powder for solution for injection has the same active substance in the same concentration (after reconstitution) and the same excipients in similar amounts as the reference medicinal product. Furthermore Bortezomib Hospira 3.5 mg powder for solution for injection has the same indications, pharmaceutical form, route of administration (the lyophilised powder enables intravenous or subcutaneous administration after reconstitution), and the same strength as VELCADE 3.5 mg powder for solution for injection.

According to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**), the waiving of bioequivalence studies is therefore deemed acceptable.

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 product under review is essentially similar to the originator product VELCADE 3.5 mg powder for solution for injection and, as outlined in Section 2.3 (Exemption), bioequivalence studies are not required. Therefore, the generic and originator products can be regarded as therapeutic equivalents and it is fully justified to transfer the information on clinical efficacy and safety from the reference product VELCADE to the bortezomib formulation under review.

2.4.6. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Bortezomib Hospira 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 3 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 3 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 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: 4.4 and 4.8 Prescription only medicine.	None proposed
Acute hypersensitivity reaction	Information on this safety concern is provided in following section of SmPC: 4.3 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 paralysis)	Information on this safety concern is provided in following sections of SmPC: 4.2, 4.4 and 4.8 Prescription only medicine.	None proposed.
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.	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Prescription only medicine.	
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 neutropenia with associated 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.
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:	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	4.2, 4.4 and 4.8 Prescription only medicine.	
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 Hospira: • 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 Prescription only medicine.	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 Hospira
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 Hospira 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 important product quality characteristics for Bortezomib Hospira, 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 Hospira is considered positive.

4. Recommendation

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Bortezomib Hospira 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.

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 Hospira in the following indications:

- Bortezomib Hospira 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 Hospira 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 Hospira 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 Hospira 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 Hospira 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 Hospira 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 Hospira (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 Hospira 3.5 mg.

The Reconstitution poster shall contain the following key elements:

- different reconstitution requirements for Bortezomib Hospira 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 Hospira 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 Hospira 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 Hospira 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 Hospira (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 Hospira plus dexamethasone, and Bortezomib Hospira plus dexamethasone and thalidomide).
- to remind that patients receiving Bortezomib Hospira 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.