21 May 2015
EMA/449381/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bortezomib Accord

International non-proprietary name: bortezomib

Procedure No. EMEA/H/C/003984/0000

Note

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

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Table of contents

List of abbreviations

CHMP	Committee for Human Medicinal Products
ECOG	Eastern Cooperative Oncology Group
ERA	Environmental Risk Assessment
HCP	Healthcare Professional
IV	Intravenous
MAH	Marketing Authorization Holder
MSL	Medical and Scientific Liaisons
NYHA	New York Heart Association
PRAC	Pharmacovigilance Risk Assessment Committee
SC	Subcutaneous
SmPC	Summary of Product Characteristics
VcTD	Velcade (bortezomib), thalidomide, dexamethasone

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare Ltd submitted on 4 June 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Bortezomib Accord, 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 20 March 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 Accord 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 Accord 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 Accord 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 data unless justified otherwise.

Information on paediatric requirements

Not applicable

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: 28-04-2004

- 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: 28-04-2004
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number: EU/1/04/274/001

Licensing status

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

1.2. Manufacturers

Manufacturers responsible for batch release

Accord Healthcare Ltd.
Sage House
319 Pinner Road
North Harrow, Middlesex
HA1 4HF
United Kingdom

Wessling Hungary Kft.
Fòti ùt 56
Budapest
1047
Hungary

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: Milena Stain

- The application was received by the EMA on 4 June 2014.
- The procedure started on 25 June 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 September 2014.
- PRAC RMP advice and assessment overview adopted by PRAC on 9 October 2014.
- During the meeting on 23 October 2014 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 23 January 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 March 2015.
- PRAC RMP advice and assessment overview adopted by PRAC on 12 March.
- During the CHMP meeting on 26 March 2015 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 20 April 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 28 April 2015.
- PRAC RMP advice and assessment overview adopted by PRAC on 7 May 2015.
- During the meeting on 21 May 2015, 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 Accord.

2. Scientific discussion

2.1. Introduction

This centralised marketing authorisation application concerns the generic product Bortezomib Accord 3.5 mg powder for solution for injection. The application is submitted under Article 10(1) ('generic' of a reference medicinal product) of Directive 2001/83/EC, as amended. The reference medicinal product is Velcade 3.5 mg powder for solution for injection, Janssen-Cilag International NV Belgium, originally authorised in the EU on 28th April 2004.

Bortezomib is a proteasome inhibitor. It is specifically designed to inhibit the chymotrypsin like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin proteasome pathway plays an essential role in regulating the turnover of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis and affects multiple signalling cascades within the cell, ultimately resulting in cancer cell death.

Bortezomib is highly selective for the proteasome. 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 applicant applied for the following indication:

Bortezomib Accord 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 Accord 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 Accord 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 agreed by the CHMP is as follows:

Bortezomib Accord 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 Accord 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 Accord 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 Accord 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 MCL indication was introduced during the assessment in order to align the PI with the extended indication of Velcade.

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 (E421).

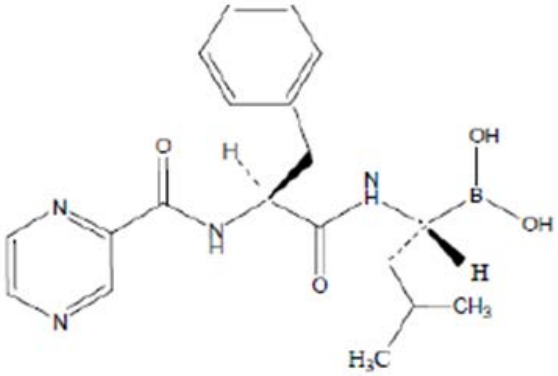
The product is available in a type I glass vial with grey chlorobutyl rubber stopper, aluminium seal, and red cap.

2.2.2. Active substance

General Information

The information on bortezomib is provided according to the Active Substance Master File (ASMF) procedure.

The chemical name of bortezomib is *N*-((1*S*)-1-benzyl-2-{[(1*R*)-1-(dihydroxyboranyl)-3-methylbutyl]amino}-2-oxoethyl)pyrazine carboxamide, also known as [(1*S*)-3-methyl-1-[[(2*R*)-3-phenyl-2-(pyrazine-2-carbonylamino) propanoyl]amino]butyl] boronic acid or {(1*R*)-3-methyl-1-[(2*S*)-3-phenyl-2-(pyrazin-2-carboxamido)propanamido]butyl} boronic acid and has the following structure and properties:



Formula: $C_{19}H_{25}BN_4O_4$ Molecular weight: 384.24

The chemical structure of bortezomib was confirmed by ^{1}H and ^{13}C NMR, FTIR spectroscopy, mass spectrometry, elemental analysis, DSC, and optical rotation.

The active substance is a white to off-white crystalline non-hygroscopic powder, very slightly soluble in water, and soluble in methanol, ethanol and DMSO.

Bortezomib contains two chiral centres and enantiomeric purity is controlled routinely by specific optical rotation. The active substance is isolated as a new polymorphic form of the boronic acid monomer with no boroxine trimer present. Bortezomib is fully dissolved and lyophilised with mannitol during finished product manufacture so polymorphic form is not important for finished product performance.

Manufacture, characterisation and process controls

Bortezomib is produced by two manufacturers in eight convergent steps from four 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.

Specification

The active substance specification includes tests for appearance, solubility, identity (FT-IR, HPLC), polymorphic form (XRPD), appearance of solution, pH (aqueous suspension), specific optical rotation (Ph. Eur.), chiral purity (chiral HPLC), water content (KF), assay (HPLC), impurities (HPLC), residual solvents (GC), bacterial endotoxins (Ph. Eur.), heavy metals (Ph. Eur.), sulphated ash (Ph. Eur.) and microbial examination (Ph. Eur. skip testing).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Analysis data on three 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 three commercial scale and three pilot scale batches of active substance from the proposed manufacturers stored in the container closure system intended for the market for up to 36 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. Photostability testing following the ICH guideline Q1B was performed on one batch. Forced degradation studies were undertaken on one batch at high temperature, and humidity in the solid state and at high temperature (60-105 ^{o}C), acidic and basic pH, and under oxidative conditions (H_2O_2).

The following parameters were tested: solid state and solution appearance, identification, aqueous pH, water content, specific optical rotation, impurities, assay, chiral purity, and bacterial endotoxins. The analytical methods used were the same as for release and were stability indicating.

No significant changes to any of the measured parameters were observed under long term or accelerated conditions. Significant degradation was observed in the photostability study, at the highest temperature, and on treatment with strong base, acid, or peroxide.

The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The aim was to develop a generic, stable formulation of bortezomib equivalent to Velcade, and with similar physico-chemical attributes. Thus, a lyophilised formulation was developed containing the same qualitative and quantitative composition both in terms of active substance and excipients.

Mannitol is a well-known pharmaceutical ingredient and its quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. The active substance forms a boronic ester with mannitol during formulation akin to the originator product. On reconstitution, an equilibrium between mannitol ester and free boronic acid is observed.

The finished product is a sterile lyophilised powder and aseptic processing was chosen to ensure sterility. Process development focused on key steps including dissolution of the active substance, sterile filtration and freeze drying. Stability of the bulk solution and compatibility with process components (vessels, atmosphere, filter) was investigated. The primary packaging is equivalent to that of Velcade and its integrity was demonstrated. The process was demonstrated to ensure sterility of the finished product. Due to the photosensitivity of bortezomib, the entire process from dissolution to packing is carried out with the exclusion of light.

The properties of the finished product after re-constitution were also investigated to ensure performance equivalent to the reference product. Solubility, photostability, pH and osmolarity of the product reconstituted in 0.9% aqueous NaCl, both in vials and syringes, were all deemed to be comparable to Velcade.

The primary packaging is a type I glass vial with grey chlorobutyl rubber stopper, aluminium seal, and red cap. 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: dissolution of bortezomib and excipients in water for injections; sterile filtration; filling into vials; lyophilisation; sealing of the vials. Sealed vials are then decontaminated by washing externally with water before placing into the commercial packaging. The process is considered to be a non-standard manufacturing process.

Major steps of the manufacturing process have been validated by three consecutive commercial scale batches of finished product. 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 this kind of dosage form and comprise tests for appearance, identification (HPLC, UV), colour, pH, clarity and sub-visible particle content of reconstituted solution (all Ph. Eur.), bacterial endotoxins (Ph. Eur.), sterility (Ph. Eur.), uniformity of dosage units (Ph. Eur.), residual *t*-butyl alcohol (GC), impurities (HPLC), assay (HPLC), water content (KF) and reconstitution time.

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 for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were analysed using the same tests as for release. The analytical procedures used are stability indicating. No significant changes to any of the measured parameters were observed.

In addition, batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is highly sensitive to even room light and should be kept away from light in its carton until use.

In-use stability studies were carried out using finished product reconstituted at room temperature (20-25 ºC) with 0.9% aqueous NaCl to 2.5 mg/ml and 1.0 mg/ml concentrations to represent those required for either subcutaneous or intravenous administration. Solutions were held in the vials or in syringes. Solutions were analysed for bortezomib content, related substances, colour and achromicity, particulate matter and pH. Results indicate that the more concentrated solution is stable for up to 8 hours in the vial and syringe, whilst the more dilute solution is stable under the same conditions for up to 3 days.

Based on available stability data, the proposed shelf-life of 3 years without special storage conditions 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 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. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

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

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Bortezomib Accord manufactured by Accord Healthcare 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.The impurity profile of Bortezomib Accord is comparable to that of the reference product VELCADE. Thus, additional toxicology studies to qualify the impurity profile of the drug product are not required.

2.3.4. Conclusion on the non-clinical aspects

In general, there are no objections to approval of Bortezomib Accord from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for powder for solution for injection containing bortezomib.

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

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

Exemption

As this is an abridged license application claiming essential similarity to a currently marketed product, no clinical studies have been undertaken to support the application.

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

According to the *Guideline on the investigation of Bioequivalence (CPMP/QWP/EWP/1401/98/Rev 1),* 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, 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.

The applicant's product Bortezomib Accord 3.5 mg powder for solution for injection has the same active substance in the same concentration and the same excipients in similar amounts as the reference medicinal product. Furthermore Bortezomib Accord 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/QWP/EWP/1401/98/Rev1)* a biowaiver for bioequivalence and clinical studies seems therefore eligible.

Clinical studies

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

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 and, as outlined in Section 2.4.1 (Exemption), bioequivalence studies are not required. Therefore, the generic and the 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.

The MCL indication was introduced during the assessment the procedure, in order to align the PI with the extended indication of Velcade.

2.4.6. Conclusions on clinical aspects

There are no objections to approval of Bortezomib Accord from a clinical point of view.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.6. 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 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC and CHMP. The CHMP endorsed the Risk Management Plan version 5 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 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

Summary of safety concerns	
	Safety in patients with ECOG>2 Second primary malignancies with VcTD induction therapy

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Heart failure	Sections 4.4, 4.8 and 5.3 of Bortezomib Accord SmPC cover information on this safety concern.	None proposed
Hepatotoxicity	Sections 4.2, 4.4 and 4.8 of Bortezomib Accord SmPC cover information on this safety concern.	None proposed
Acute hypersensitivity reaction	Sections 4.3 and 4.8 of Bortezomib Accord SmPC cover information on this safety concern.	None proposed
Tumour lysis syndrome	Sections 4.4 and 4.8 of Bortezomib Accord SmPC cover information on this safety concern.	None proposed.
Peripheral motor neuropathy (including paralysis)	Sections 4.2, 4.4 and 4.8 of Bortezomib Accord SmPC cover information on this safety concern.	None proposed.
Autonomic neuropathy	Sections 4.2, 4.4 and 4.8 of Bortezomib Accord SmPC cover information on this safety concern.	None proposed.
Acute diffuse infiltrative pulmonary disease	Sections 4.3, 4.4 and 4.8 of Bortezomib Accord SmPC cover information on this safety concern.	None proposed.
Pericardial disease	Sections 4.3 and 4.8 of Bortezomib Accord SmPC cover information on this safety concern.	None proposed.
Pulmonary hypertension	Section 4.8 of Bortezomib Accord SmPC covers information on this safety concern.	None proposed.
Herpes zoster infection	Sections 4.4 and 4.8 of Bortezomib Accord SmPC cover information on this	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	safety concern.	
Posterior reversible encephalopathy syndrome	Sections 4.4 and 4.8 of Bortezomib Accord SmPC cover information on this safety concern.	None proposed.
Optic neuropathy and different degrees of visual impairment (up to blindness)	Section 4.8 of Bortezomib Accord SmPC covers information on this safety concern.	None proposed.
Thrombocytopenia and thrombocytopenia with associated bleeding	Sections 4.2, 4.4, 4.8 and 4.9 cover information on this safety concern.	None proposed.
Neutropenia and neutropenia with associated infection	Sections 4.2, 4.4 and 4.8 cover information on this safety concern.	None proposed.
Progressive multifocal leukocencephalopathy	Section 4.4 of Bortezomib Accord SmPC covers information on this safety concern.	None proposed.
Ventricular rhythm abnormalities	Section 4.8 of Bortezomib Accord SmPC covers information on this safety concern.	None proposed.
Guillain-Barré syndrome	None risk minimisation activities are proposed at this time.	None proposed.
Other central nervous system disorders	Section 4.8 of Bortezomib Accord SmPC covers information on this safety concern.	None proposed.
Medication/dispensing errors	Sections 4.2, 4.4 and 6.6 cover information on this safety concern.	In order to prevent medication errors, IV administered SC or vise a versa as well as drug administration and dosing errors, MAH will provide educational materials (reconstitution, dosing and administration booklet, reconstitution poster and a dosing slide rule) to HCPs, MAH will also provide training to medical representatives, medical and scientific liaisons (MSLs) and medical information personnel for medication/dispensing errors. In order to prevent confusion with administering the incorrect regimens

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
		in the transplant induction setting, MAH will provide proper training to all MSLs on the different bortezomib treatment schedules approved for transplant induction. MSLs will be able to offer on-site training and relevant recommendations. An educational programme and specific tools for HCPs will be developed who are involved in the prescription and administration of bortezomib combination regimens in the transplant induction.
Safety in patients with cardiac impairment or with NYHA Class III or IV impairment	Section 4.4 of Bortezomib Accord SmPC covers information on this safety concern.	None proposed.
Safety in patients with ECOG>2	None risk minimisation activities are proposed at this time.	None proposed.
Second primary malignancies with VcTD induction therapy	Section 4.4 of Bortezomib Accord SmPC covers information on this safety concern.	None proposed.

2.7. PSUR submission

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

2.8. Product information

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Velcade. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of Bortezomib powder for solution for injection. The reference product Velcade has the following indications:

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.

The MCL indication was introduced during the assessment, in order to align the PI with the extended indication of Velcade.

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

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

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.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of Bortezomib Accord in the following indication

Bortezomib as monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone is indicated for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation.

Bortezomib in combination with melphalan and prednisone is indicated for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

Bortezomib in combination with dexamethasone, or with dexamethasone and thalidomide, is indicated for the induction treatment of adult patients with previously untreated multiple myeloma who are

eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

Bortezomib in combination with rituximab, cyclophosphamide, doxorubicin and prednisone is indicated for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for haematopoietic stem cell transplantation.

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**

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and 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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **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 Accord 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 Accord 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 Accord (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 Accord 3.5 mg.

The Reconstitution poster shall contain the following key elements:

- different reconstitution requirements for Bortezomib Accord 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 Accord 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 Accord 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 Accord 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 Accord (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 Accord plus dexamethasone, and Bortezomib Accord plus dexamethasone and thalidomide).
- to remind that patients receiving Bortezomib Accord in combination with thalidomide should adhere to the pregnancy prevention programme of thalidomide, with reference to the SmPC of thalidomide for additional information.