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Public Assessment Report

Scientific discussion

Bortezomib Logenex & Bortega
Bortezomib (as mannitol boronic ester)

NO/H/0244/001/DC & NO/H/0252/001/DC

Date: 10.082015

This module reflects the scientific discussion for the approval of Bortezomib Logenex and Bortega. The procedures were finalised at day 210 12.06.2015. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Bortezomib Logenex, Powder for solution for injection, 3.5 mg and Bortega, Powder for solution for injection, 3.5 mg from Logenex Pharma and Heaton k.s., respectively.

The products are indicated for*:*

"[Product name] as monotherapy or in combination with pegylated liposomal doxorubicin 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.

[Product name] 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.

[Product name] 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."

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

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

Bortezomib is a proteasome inhibitor (Antineoplastic agents, L01XX32). It blocks the proteasome, which is a system within the cells that breaks down proteins when they are no longer needed. When the proteins in the cancer cells, such as the proteins that control the growth of the cells, are not broken down, the cells are affected and they eventually die.
It is used to treat adults with multiple myeloma, a cancer of the plasma cells in the bone marrow.

Please refer to section VI for conditions under Article 21a/22 of Directive 2001/83.

II. QUALITY ASPECTS

II.1 Introduction

The drug product Bortezomib Logenex / Bortega, powder for solution for infusion, is a sterile white to off white powder for solution for injection filled in clear glass vials closed with rubber stoppers and aluminium caps.

The drug product contains the active substance bortezomid, and is a generic equivalent to Velcade powder for solution for injection marketed by Janssen-Cilag International NV.

II.2 Drug Substance

The active substance bortezomib is manufactured by Teva Czech Industries s.r.o., Czech Republic. No Ph. Eur. monograph is available for this active substance.

The manufacturing process, is in general well described and consists of six synthetic steps followed by a purification (re-crystallization) step; it has been shown that sufficient control of significant impurities is covered by GMP.

In general acceptable specifications are set for the drugs substance, with adequately described and sufficiently validated analytical methods.

Three production batches of bortezomib have been manufactured, analysed and put on stability studies. Data from the stability studies support the proposed retest period of 24 months when stored in the container closure system described in the dossier, under frozen conditions (-20 °C ± 5 °C).

II.3 Medicinal Product

The development of the drug product has been described. The dosage form and composition have been chosen to secure essential similarity with the originator product. The development of the manufacturing process, the choice of the container closure system, and the physicochemical and biological properties of the drug product have been adequately described. The stability of the reconstituted drug product as claimed in the product information is satisfactorily documented.

The drug product is manufactured by PharmIdea SIA, Latvia. The manufacturing process is non-standard and involves manufacture of lyophilised sterile product using aseptic techniques. The manufacturing process and process controls have been sufficiently described, and is supported by the process validation on three production scale batches.

Acceptable specifications have been established for the excipients, components used that are removed during manufacture, and also for the primary packaging materials.

The drug product specifications cover appropriate parameters for this dosage form, and acceptable limits are proposed. The analytical procedures are adequately described, and method validation in compliance with ICH guideline is presented for relevant methods. Batch analysis has been performed on three production scale batches. The results show that the finished product meets the specifications proposed.

Stability studies according to ICH guideline have been presented, and all results from six months storage at the accelerated condition and 12 months storage at intermediate and long term conditions are well within the proposed shelf-life specification.

The proposed shelf-life of 2 years for unopened vials without any temperature storage restriction is supported by the stability data presented. The product should be kept in the outer carton in order to protect from light.

The quality aspects are considered adequately documented.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Agreement between member states was reached during a written procedure. The application was considered approvable from a quality point of view.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of bortezomib are well known. As bortezomib is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

The application for Bortezomib Logenex / Bortega 3.5 mg powder for solution for injection concerns generic variations of bortezomib. The reference product Velcade was approved before the finalisation of the present Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00). Consequently, there is no ERA for Velcade.
An ERA for bortezomib has been submitted as part of the MAA for Bortezomib Logenex / Bortega, written by Ivo Beikmanis.

Summary of main study results

Substance (INN/Invented Name): bortezomib			
CAS-number (if available): 179324-69-7			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	Experimental method not provided	1.9	Potential PBT: No
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\ water}$, default	0.32	µg/L	> 0.01 threshold

			Yes
PEC $_{surface\ water}$, refined (e.g. prevalence, literature)	6.0×10^{-9}	µg/L	> 0.01 threshold No

The log octanol/water partition coefficient (log K_{ow}) of bortezomib is 2 at pH 7-7.4. This is below the trigger value of 4.5 (EMEA/CHMP/SWP/4447/00), and a screening for persistence bioaccumulation and toxicity is therefore not required.

Predicted Environmental Concentration for surface water ($PEC_{surface\ water}$) is 0.32 µg/l. Based on prevalence data for the indication multiple myeloma in Norway, the member state included in the registration procedure with the highest prevalence data, a refined $PEC_{surface\ water}$ is calculated to orders of magnitude below the threshold value of 0.01 µg/l, indicating that no further testing is required.

Conclusion on ERA:
Considering the above data, bortezomib is not expected to pose a risk to the environment.

III.3 Discussion on the non-clinical aspects

Agreement between member states was reached during a written procedure. The application was considered approvable from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

No new data have been submitted and no bioequivalence studies have been conducted.

IV.2 Pharmacokinetics

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

According to the applicant Bortezomib Logenex / Bortega contains the same concentration of the same active substance and the same excipients in similar amounts as the currently approved reference product Velcade.

The following table is from the Non-Clinical Overview:

Table 1: Comparison of the composition of reference product with Bortezomib 3.5 mg powder for solution for injection

Ingredients	Velcade®	Bortezomib
Active substance:		
Bortezomib (as a mannitol boronic ester)	3.5 mg	3.5 mg
Excipients:		
Mannitol	45 mg	45 mg
Nitrogen, low oxygen**	-	q.s.

Nitrogen is commonly used in order to displace air from solutions subject to oxidation, by sparking, and to replace air in the headspace above the product in their final packaging. Since nitrogen is insoluble in water and other solvents as well, it remains separated from the actual pharmaceutical formulation as product.
Further dilution is obtained with 1.4 ml (for subcutaneous injection) or 3.5 ml (for intravenous injection) of 0.9% sodium chloride solution for injection without preservatives.

The medicinal products Bortezomib Logenex / Bortega and Velcade are aqueous intravenous (i.v.)/subcutaneous (s.c.) solutions, both of them contains the same excipients in similar amounts, and the excipients does not interact and/or otherwise affect the disposition of the drug substance. Bortezomib Logenex / Bortega can therefore be considered bioequivalent to the reference product Velcade and no bioequivalence studies are deemed necessary.

IV.3 Pharmacodynamics

N/A

IV.4 Clinical efficacy

N/A

IV.5 Clinical safety

N/A

IV.6 Risk Management Plan

The following introductory statement may be used
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Bortezomib Logenex and Bortega.

V.3 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk		
Heart failure	The risk is adequately addressed and communicated in SPC sections 4.4 and 4.8.	None proposed
Hepatotoxicity	The risk is adequately addressed and communicated in SPC sections 4.2; 4.4 and 4.8.	None proposed
Acute hypersensitivity reactions	The risk is adequately addressed and communicated in SPC sections 4.3 and 4.8.	None proposed
Tumour lysis syndrome	The risk is adequately addressed and communicated in SPC sections 4.4 and 4.8.	None proposed
Peripheral motor neuropathy (including paralysis)	The risk is adequately addressed and communicated in SPC sections 4.2; 4.4 and 4.8.	None proposed
Autonomic neuropathy	The risk is adequately addressed and communicated in SPC sections 4.4 and 4.8.	None proposed
Acute diffuse infiltrative pulmonary disease	The risk is adequately addressed and communicated in SPC sections 4.3; 4.4 and 4.8.	None proposed
Pericardial disease	The risk is adequately addressed and communicated in SPC sections 4.3 and 4.8.	None proposed
Pulmonary hypertension	The risk is adequately addressed and communicated in SPC section 4.8.	None proposed
Herpes zoster infection	The risk is adequately addressed and communicated in SPC sections 4.4 and 4.8.	None proposed
Posterior reversible encephalopathy syndrome (PRES)	The risk is adequately addressed and communicated in SPC sections 4.4 and 4.8.	None proposed
Optic neuropathy, different degrees of visual impairment (up to blindness)	The risk is adequately addressed and communicated in SPC section 4.8.	None proposed
Important potential risk		
Progressive multifocal leukoencephalopathy	The risk is adequately addressed and communicated in SPC section 4.4.	None proposed
Ventricular rhythm abnormalities	The risk is adequately addressed and communicated in SPC sections 4.4 and 4.8.	None proposed
Guillain–Barré syndrome	None – should PhV activities uncover additional data risk minimisation measures will be developed	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Other central nervous system disorders	The risk is adequately addressed and communicated in SPC section 4.8.	None proposed
Medication / dispensing errors	The risk is adequately addressed and communicated in SPC sections 4.2; 4.4 and 6.6. Subject to restricted medical prescription Use restricted to physician qualified and experienced in the use of chemotherapeutic agents Single vial packaging, labelling on the vial label for guidance against medication/dispensing errors and single labelling for intravenous and subcutaneous routes of administration	Educational material for HCPs involved in the prescribing, dispensing, handling or administration of bortezomib (particularly oncologists, haematologists, haematology nurses, oncology nurses, hospital pharmacists, and other specialised personnel in charge of preparing chemotherapeutic drugs) consisting of: SPC; Reconstitution, dosing and administration booklet; Reconstitution poster; Dosing slide rule; Induction transplant regimens graph.
Missing information		
Safety in patients with cardiac impairment or with NYHA Class III or IV impairment	Labelled in SPC section 4.4.	None proposed
Safety in patients with ECOG>2	None – should PhV activities uncover additional data risk minimisation measures will be developed	None proposed
Second primary malignancies with VcTD induction therapy	Labelled in SPC section 4.4.	None proposed

IV.7 Discussion on the clinical aspects

The application contains an adequate review of published non-clinical and clinical data.
Bortezomib Logenex / Bortega are indicated for parenteral use only.

According to the applicant Bortezomib Logenex / Bortega contains the same concentration of the same active substance and the same excipients in similar amounts as the currently approved reference product Velcade.

Agreement between member states was reached during a written procedure. The application was considered approvable from a clinical point of view.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Bortezomib PharmIdea, The readability testing (Bortezomib Pharmidea) was performed in June 2013 on a PIL identical to that of the reference product (Velcade).
The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The conclusion of the benefit risk assessment is positive.

Proposed list of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC:

- **Additional risk minimisation measures (including educational material)***

In each Member State, the Marketing Authorisation Holder (MAH), which will intend to place the medicinal product on the market, 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 Logenex are provided with educational material.

The educational material shall consist of the following key elements:
• SPC
• Reconstitution, dosing and administration booklet
• Reconstitution poster
• Dosing slide rule
• Induction transplant regimens graph
The information provided in educational material shall contain the key elements described in Annex 11 (see below)*.

* Applies to both Bortezomib Logenex and Bortega.

Annex 11 in RMP (RMP-LOG-BOR-v02)
Mock-up of proposed additional risk minimisation measures*

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

- Bortezomib Logenex 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 Logenex (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 Logenex

The Reconstitution poster shall contain the following key elements:

- different reconstitution requirements for Bortezomib Logenex 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 Logenex 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 Logenex

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 Logenex 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 Logenex (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 Logenex plus dexamethasone, and Bortezomib Logenex plus dexamethasone and thalidomide)
- to remind that patients receiving VELCADE in combination with thalidomide should adhere to the pregnancy prevention programme of thalidomide, with reference to the SPC of thalidomide for additional information